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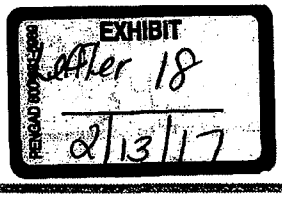

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RESEARCH ARTICLE

Gastrointestinal Disorder Associated with Olmesartan Mimics Autoimmune Enteropathy

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Abstract

Background and Objectives

Anti-hypertensive treatment with the angiotensin II receptor antagonist olmesartan is a rare cause of severe Sprue-like enteropathy. To substantiate the hypothesis that olmesartan interferes with gut immune homeostasis, clinical, histopathological and immune features were compared in olmesartan-induced-enteropathy (OIE) and in autoimmune enteropathy (AIE).

Methods

Medical files of seven patients with OIE and 4 patients with AIE enrolled during the same period were retrospectively reviewed. Intestinal biopsies were collected for central histopathological review, T cell Receptor clonality and flow cytometric analysis of isolated intestinal lymphocytes.

Results

Among seven olmesartan-treated patients who developed villous atrophy refractory to a gluten free diet, three had extra-intestinal autoimmune diseases, two had antibodies reacting with the 75 kilodalton antigen characteristic of AIE and one had serum anti-goblet cell antibodies. Small intestinal lesions and signs of intestinal lymphocyte activation were thus reminiscent of the four cases of AIE diagnosed during the same period. Before olmesartan discontinuation, remission was induced in all patients (7/7) by immunosuppressive drugs.

mitochondria, -LKM1, -smooth muscle, -thyroid) and serological tests of celiac disease (serum immunoglobulin IgA (AGA) and IgG (AGG) anti-gliadin antibodies, serum IgA class endomysial antibodies (EMA), serum anti-human tissue transglutaminase IgA (tTG) antibodies) were also recorded. HLA-DRB1 and DQB1 genotyping was performed by hybridization with sequence-specific oligonucleotides following amplification by PCR, using the InnoLipa HLA genotyping test (Abott, Rungis France) [7]. Endoscopic evaluation included upper gastrointestinal endoscopy or enteroscopy with gastric and small intestinal biopsies, colonoscopy with colonic biopsies. Clinical response was defined by a reduction of 50% of stool frequency and recovery of at least 50% of body weight loss. Mucosal response was defined by total or partial recovery of a normal villous epithelium [8].

For histological analysis, gastrointestinal specimens were fixed in 10% formalin, embedded in paraffin, and 5 μm sections stained with H&E and Giemsa. Villous atrophy was assessed on two to 3 duodenal biopsies as described [9]. Duodenal lymphocytosis was defined by counts of intraepithelial lymphocytes (IEL) over 30 per 100 duodenal epithelial cells (EC), lymphocytic gastritis by IEL counts over 25 per 100 gastric columnar EC and lymphocytic colitis by IEL counts over 20 per 100 surface colonic EC. Apoptotic bodies (single-cell karyorrhectic debris) were assessed and were enumerated per 10 crypts [9].

Isolation of IEL, lamina propria lymphocytes (LPL) and peripheral blood lymphocytes (PBL) was performed as described [8, 10, 11]. Surface Lymphocyte phenotype was assessed by 8-color flow-cytometry. Briefly, pellets of 2-5x10^4 cells were incubated for 20 minutes with mixof antibodies directly conjugated with FITC, APC, PE, PE/Cy7 BD-Horizon-V450, PerCP/Cy5.5, AmCyan, APC-H7 at optimal concentrations. The following antibodies were used: CD45, CD3, CD4, CD8, NKP46, CD56, CD57, NKG2A, control isotypes (BD Biosciences, Le Pont de Claix, France), CD103, NKG2C, CD94, TCRαβ, TCRγδ (Beckman Coulter, Nyon, Switzerland) and NKG2C (R&D system, Abingdon, UK). For intracellular FOXP3 detection, cells were surface labeled with CD45, CD4 and CD25, and then fixed, permeabilized using Human FOXP3 Buffer Set (BD Biosciences) and labelled with PE-conjugated anti-human or control isotype (BD Biosciences). Fluorescence staining was analyzed with a FACSCanto II flow cytometer using the DIVA software (BD Biosciences) and gated on $CD45^+$ cells.

Molecular detection of clonal TCRγ chains rearrangements was performed on DNA extracted from frozen specimens and from PBL by multiplex PCR and confirmed by analysis of heteroduplex formation, as described [8].

Ethics Statement

The study was approved by the Ile-de-France II ethical committee (Paris, France).

Results

Clinical and immunological characteristics (Table 1)

Seven patients treated by olmesartan were referred to our medical center between 2000 and 2014 for unexplained severe enteropathy with villous atrophy refractory to a gluten free diet (Table 1). All had chronic diarrhea with malnutrition. Four of them (patients 1, 2, 4 and 5) were treated by parenteral nutrition at time of admission and two patients had already been hospitalized for severe hypokalemia (patients 1 and 4). Three patients had extra-intestinal autoimmune diseases. Four patients had the celiac HLA-DQ2/DQ8 susceptibility genotype. Celiac antibodies (IgA and IgG anti-gliadin and anti-transglutaminase, IgA anti-endomysium) were tested before initiating a gluten free diet and were negative except in one HLA-DQ2 patient (patient 1) who had low titers of serum IgA anti-transglutaminase (Table 1). Primary immunoglobulin deficiency was eliminated in all patients.

Table 1. Clinical and immune characteristics.

Case	Sex	Age (y)	Autoimmunediseases	BMI	DQ2/8	Anti AIE 75 kDa	anti-E	tTG	IGA	ANA	Duod	Lymphocytosis		
												Duod	Sto	Col
Olmesartan														
1	F	74	Goujerot Sjogren	17	+	+	*nd*	+	-	+	TVA	30%	-	-
2	F	72	-	23	*nd*	+	*nd*	-	-	*nd*	STVA	40%	-	-
3	F	69	Uveitis Cholangitis	17	+	-	-	-	*nd*	+	STVA	40%	-	-
4	M	79	-	20	+	-	-	-	*nd*	+	TVA	30%	-	-
5	M	60	-	21	-	-	-	-	*nd*	-	TVA	100%	+	-
6	F	65	Cholangitis	20	-	-	*nd*	-	-	+	TVA	30%	-	-
7	M	77	-	24	+	*nd*	-*	-	-	*nd*	STVA	30%	-	-
Mean		**71**		**20**	**67%**	**33%**	**0%**	**14%**	**0%**	**80%**		**43%**	**14%**	**0**
AIE														
8	F	17	Auto I Pancreatitis anti-phospholipid Sd Polyarthritis	16	+	+	*nd*	-	-	+	TVA	40%	-	-
9	F	23	-	21	-	+	+	-	-	+	TVA	90%	+	+
10	F	19	-	20	-	+	-	+	-	*nd*	STVA	57%	-	+
11	F	41	-	18	-	+	*nd*	+	+	+	STVA	65%	-	-
Mean		**25**	**25%**	**19**	**25%**	**100%**	**50%**	**50%**	**25%**	**100%**		**63%**	**25%**	**50%**

*: detection of serum anti-goblet cells antibodies.

Ab: antibody. Anti-E: anti-enterocyte Ab. ANA: anti-nuclear Ab. BMI: Body Mass Index. Col: colon. Duod: duodenum. EMA: IgA anti-endomysium. IGA: IgA anti-gliadin. Lymphocytosis: number of intraepithelial lymphocytes for 100 epithelial cells. LC: lymphocytic colitis. LG: lymphocytic gastritis. Sto: stomach. tTG: IgA anti-transglutaminase. VA: villousatrophy. TVA: total villousatrophy. ST VA: sub-totalvillousatrophy. PVA: partial villousatrophy. y: years. Noserum anti-tTG IgG or antigliadin IgG was found. No IgA anti-endomysium was found.

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Serum antibodies reacting with goblet cells or with the brush border 75-kilodalton antigen (AIE-75KD) were detected in one (1/4) and 2 patients (2/6), respectively. Serum anti-nuclear antibodies were detected in 4 patients (4/5).

Histopathological findings (Fig 1)

Duodenal or jejunal biopsies showed subtotal (patients 2, 3 and 7) or total villous atrophy (patients 1,4, 5 and 6), dense lymphocyte and plasma cell *lamina propria* infiltration and crypt rarefaction (patients 1–7), paucity of goblet cells and glandular apoptosis (patients 2 and 4). Such intestinal pathological features were reminiscent of those observed in 4 patients with adult autoimmune enteropathy (AIE) investigated during the same period (Fig 1). An intestinal collagenous subepithelial layer thicker than 10μm was observed in patient 1, as in one AIE patient (patient 9). Patient 4 had very high numbers of IEL in the duodenum (100%) and displayed lymphocytic gastritis. Similarly, two AIE patients (9 and 10) with increased numbers of duodenal IEL also had lymphocytic gastritis and/or colitis (Table 1).

Lymphocyte isolation and flow cytometry analysis (Tables 2, 3 and 4)

Yield of isolated IEL was low or normal in all patients with OIE and AIE (0.1–0,3x10^6/6 duodenal biopsies) except for patient 11 with AIE complicated by a $CD4^+$ lymphoma which infiltrated the gut epithelium. In contrast, and in keeping with *lamina propria* infiltration in tissue sections, the yield of LPL was increased (0,8 à 1.5x10^6/ 6 duodenal biopsies, normal 0.5 ±0.1). Flow cytometry analysis showed a predominance of CD3+ TCRαβ+T cells in IEL and

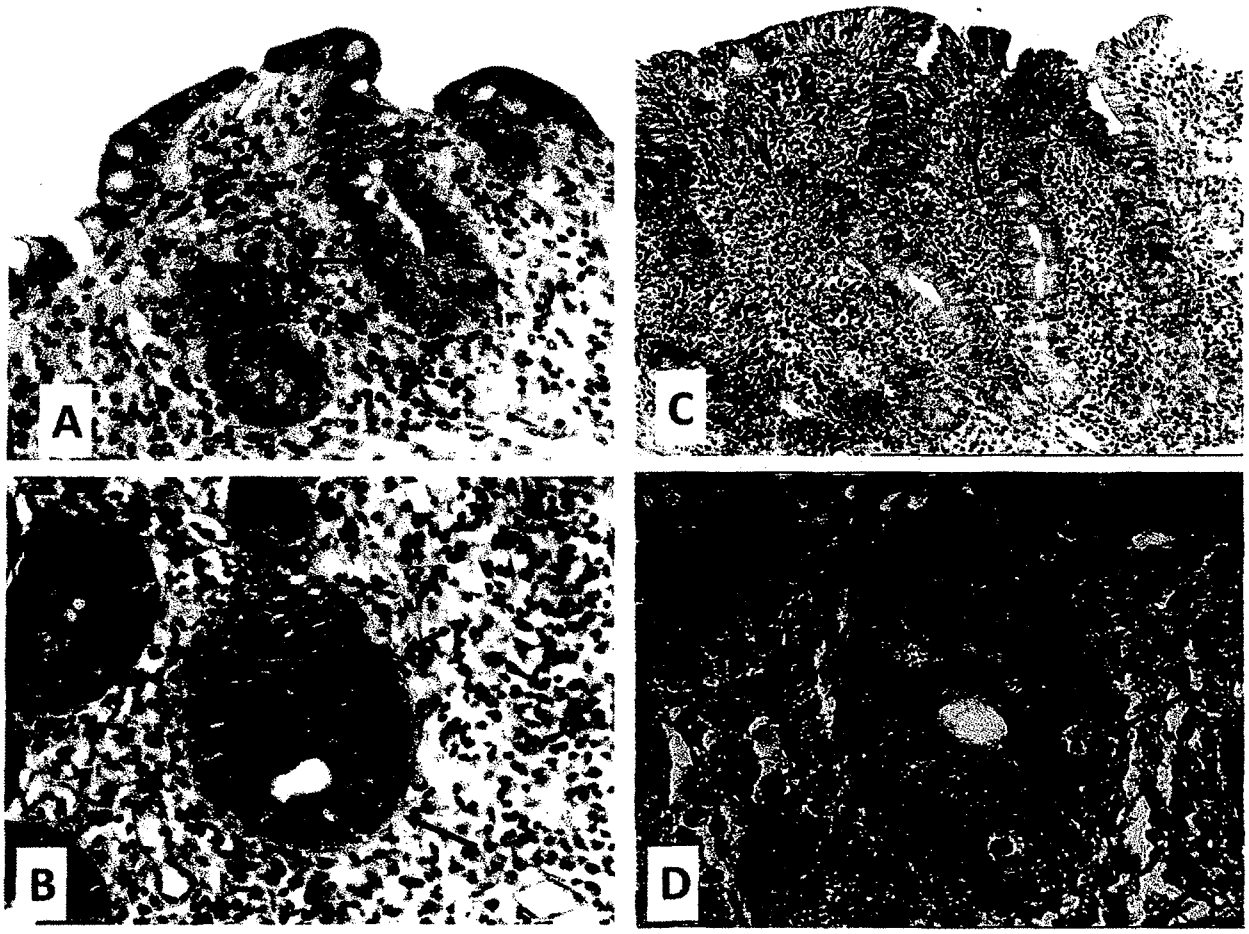

Fig 1. H&E staining of the duodenal biopsies of one patient treated with Olmesartan (patient 2) (A, B) and of one patient with AIE (patient 7) (C, D) showing subtotal villous atrophy (A, C: original magnification x 100) with glandular apoptosis (B, D: original magnification x200).

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LPL. In contrast with observations in celiac disease, the frequency of γδT IEL was low in both OIE and AIE, while the frequency of CD4+ IEL was often high in OIE. A very high count of CD4+ IEL cells was observed in patient 10, who had AIE complicated by a CD4+small cell T lymphoma which infiltrated the epithelium. In some OIE and AIE patients, T cells expressing the CD57 or NKG2C NK markers were increased in epithelium and *lamina propria*, suggesting chronic activation. Interestingly, the frequency of the normal subset of IEL lacking surface CD3 and expressing the NK marker NKP46 was higher in patients with OIE than with AIE (Table 2), even if the difference was not statistically significant. The frequency of CD3- IEL remained however within normal values, thus eliminating type II refractory CD (Tables 2 and 3) [10]. No deficit in the number of intestinal and blood regulatory T cells CD4+CD25 +FOXP3+ was found either in OIE or in adult AIE (Tables 3 and 4). No clonal rearrangement of T cell receptor gamma was found in intestinal mucosa of patients treated with olmesartan, while two out of four adult AIE displayed either an oligoclonal (patient 9) or clonal (patient 11) repertoire [5,6].

Table 2. Phenotype of intestinal intraepithelial lymphocytes.

Case	CD103+		CD8+	CD4+	TCR		CD94+	CD56+	CD57+	NKP46	NKG2A	NKG2C
	CD3+	CD3-			αβ	γδ						
Olmesartan												
1	71%	2%	67%	30%	86%	5%	20%	-	3%	3%	5%	5%
2	60%	21%	63%	23%	74%	3%	-	44%	-	26%	-	10%
3	69%	23%	64%	11%	59%	12%	27%	37%	16%	37%	17%	3%
4	83%	5%	66%	35%	92%	2%	46%	5%	18%	6%	5%	8%
5	47%	30%	54%	19%	64%	6%	20%	10%	24%	35%	7%	80%
6	53%	14%	46%	29%	72%	4%	16%	11%	9%	12%	10%	7%
Median	**65%**	**17%**	**64%**	**26%**	**73%**	**4%**	**20%**	**11%**	**16%**	**19%**	**7%**	**7%**
AIE												
8	71%	5%	70%	24%	85%	2%	64%	22%	2%	6%	5%	80%
9	79%	1%	80%	4%	95%	3%	27%	3%	10%	-	-	-
10	88%	4%	90%	4%	94%	0%	8%	6%	7%	1%	-	-
11	93%	3%	40%	60%*	88%	8%	13%	2%	1%	7%	4%	5%
Median	**84%**	**4%**	**75%**	**14%**	**91%**	**3%**	**20%**	**5%**	**5%**	**6%**	**4%**	**48%**
Normal value (%)	**80–95**	**2–20**	**60–85**	**5–15**	**70–88**	**12–20**	**16–38**	**9–19**	**0**	**5–15**	**11–38**	**1–5**

*: excess of CD4+ IEL with onset of CD4 lymphoma after two years treatment with azathioprine (Case published in Malamut et al, ClinGastHepatol 2014); flow cytometry analysis of AIE onset is not available.

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Outcome of olmesartan-induced enteropathy (Table 5)

Patients were treated with olmesartan for 2 to 10 years at a mean dosage of 20mg/day at onset of diarrhea. Following diagnosis of villous atrophy resistant to a gluten free diet, they received steroids and immunosuppressors (Table 5). In all but one (patient 4), steroids and immunosuppressors were introduced before olmesartan discontinuation (Table 5). Treatment with anti-TNF-αantibodies induced clinical response in 5 patients (5/6) with partial villous recovery

Table 3. Phenotype of lamina propria intestinal lymphocytes.

Case	CD103+ CD3+	CD103- CD3+	CD8+	CD4+	TCR alpha beta	CD19+	CD94+	CD56+	CD57+	NKG2C	CD4+ CD25+ FOXP3+
Olmesartan											
1	34%	52%	35%	53%	80%	8%	3%	-	1%	3%	5%
2	25%	53%	50%	45%	74%	-	-	42%	-	6%	6%
3	28%	62%	39%	51%	84%	8%	12%	5%	10%	-	6%
4	23%	66%	38%	56%	85%	8%	17%	1%	11%	1%	11%
5	42%	39%	47%	38%	73%	8%	3%	5%	30%	17%	4%
6	26%	52%	37%	39%	68%	23%	10%	2%	9%	5%	10%
Median	**27%**	**53%**	**39%**	**48%**	**77%**	**8%**	**10%**	**5%**	**10%**	**5%**	**6%**
AIE											
8	23%	49%	40%	38%	73%	18%	24%	14%	5%	3%	8%
9	54%	45%	55%	38%	-	-	-	-	-	-	4%
10	38%	57%	47%	49%	94%	5%	7%	6%	8%	-	8%
11	38%	75%	33%	54%	83%	1%	27%	10%	5%	16%	1%
Median	**38%**	**53%**	**43%**	**44%**	**83%**	**5%**	**24%**	**10%**	**5%**	**10%**	**6%**
Normal Value (%)	**20–35**	**40–70**	**30–50**	**40–60**	**65–85**	**5–10**	**<8**	**<10**	**<1**	**<0,5**	**2–12**

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Table 4. Phenotype of peripheral blood lymphocytes.

Case	CD103+ CD3-	CD3+ CD8+	CD3+ CD4+	TCR alpha beta	CD19+	CD94+	CD56+	CD57+	NKG2C	LT CD4+ CD25+ FOXP3+
Olmesartan										
1	0.5%	10%	49%	-	11%	-	-	-	-	3%
2	0.5%	8%	63%	69%	-	-	52%	-	-	5%
3	0.1%	25%	50%	71%	17%	15%	13%	16%	-	3%
4	0.1%	13%	62%	-	30%	-	-	-	1%	4%
5	-	19%	47%	-	6%	-	-	-	6%	6%
6	0.1%	37%	39%	81%	8%	-	8%	16%	0%	1%
Median	**0.1%**	**16%**	**50%**	**71%**	**11%**	**15%**	**13%**	**16%**	**1%**	**4%**
AIE										
8	0.0%	34%	39%	68%	7%	23%	57%	31%	73%	4%
9	0.4%	38%	50%	-	-	30%	20%	26%	-	-
10	0.0%	30%	61%	87%	4%	6%	11%	19%	-	4%
11	0.2%	22%	61%	78%	1%	12%	5%	13%	3%	3%
Median	**0.1%**	**32%**	**55%**	**78%**	**4%**	**17%**	**16%**	**23%**	**38%**	**4%**
Normal Value (%)	**<1**	**30–50**	**40–60**	**65–85**	**5–20**	**5–25**	**5–25**	**5–25**	**0**	**2–12**

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in 3 patients (3/6). FK-506 and rapamycin were used in patient 1, who had collagenous-like sprue and induced complete clinical and histological recovery with disappearance of the collagenous subepithelial layer. After olmesartan discontinuation, remission was maintained despite withdrawal of immunosuppressive drugs in patients 1, 2, 5 and 6. Complete mucosal recovery was confirmed on control intestinal biopsies performed 2 to 7 months later and these patients remain in clinical remission at latest follow-up, one year after cessation of immunosuppression interruption. Patient 4 had stopped olmesartan six months before admission as hypertension had resolved because of the severe diarrhea. Despite this, diarrhea persisted, with important potassium loss that required intravenous supplementation and prolonged hospitalization. Steroids given intravenously were inefficient but infusion of anti-TNF-αantibodies

Table 5. Treatments.

	Steroids	AZA/6MP	Anti-TNF-α	Cyclosporin	Rapamycin	FK-506	Rituximab
Olmesartan							
1	10 m:-/ -	4m:-/-	1 m:-/-	-	2m: +/+	8m: +/+	-
2	12m: +/+	6m:-/nd	30 m: +/-	-	-	-	-
3	6m: +/ nd	48 m: +/nd	-	-	-	-	-
4	2 m:-/nd	-	12m: +/+	-	-	-	-
5	1m:-/nd	-	6m: +/-	-	-	-	-
6	12m: +/nd	12m: +/nd	12m: +/+	-	-	1m:-/nd	-
7	12m: +/+	-	12m: +/+	-	-	-	-
AIE							
8	2m:-/-	1m:-/-	9m:-/-	36m: +/+	-	-	-
9	47m: +/+	114m: +/-	2m:-/-	-	-	-	1m:-/-
10	15m:-/ nd	2m:-/nd	10 m: +/-	12m: +/+	-	-	nd
11	6m:-/nd	14m: +/+	-	-	-	-	1m:-/-

m: month. AZA: azathiopurin. 6MP: 6 mercaptopurin. clinical response (+ or-) / mucosal effect (+/-)

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rapidly induced clinical remission. Mucosal healing was observed after seven months of treatment and no relapse was observed after two years without any immunosuppressive treatment. Patient 7 was already treated with anti-TNF-α at time of olmesartan interruption. Despite olmesartan discontinuation, diarrhea relapsed after anti-TNF-α withdrawal but remission was restored when anti-TNF-αtherapy was resumed. Three months after olmesartan discontinuation, he is still treated with anti-TNF-α. Despite being informed of the risks, patient 3 has not stopped olmesartan and still needs azathioprine to control diarrhea.

Discussion

During the past three years, several cases of severe enteropathy were described in association with olmesartan [2, 12]. A recently published six year-review of pathology reports of patients investigated in the US showed no association between the use of olmesartan and the histological diagnosis of celiac disease or microscopic colitis, respectively [13] suggesting that this severe gastrointestinal disorder is a rare adverse effect of this angiotensin receptor-blocker. Our observations further suggest that OIE affects predisposed individuals. As already reported by Rubio-Tapia, we observed an increased prevalence of the HLA-DQ2/DQ8 genotype (67%), which predisposes to celiac disease or to type I diabetes. In support of our hypothesis, extra-intestinal autoimmune diseases were found in 3/7 patients.

The olmesartan prodrug is converted within the small bowel into olmesartan medoxomil, the active compound, which binds the angiotensin 2 receptor AT1 [14, 15, 16]. How olmesartan can induce severe inflammation and intestinal damage remains to be elucidated. In keeping with the hypothesis of an immune mechanism, OIE referred to our institution shared striking similarities with AIE. In both situations, severe villous atrophy was associated with glandular apoptotic lesions and increased numbers of intestinal T cells expressing the NK markers CD57 or NKG2C. Antinuclear and anti-AIE-75KD or anti-goblet cells antibodies were found in respectively 80% and 43% of patients. Moreover, all patients with OIE responded to immunosuppressive drugs. Cases of patients 4 and 7 are particularly informative, as anti-TNF-α therapy was necessary to achieve remission of a self-sustaining enteropathy after olmesartan discontinuation. It suggests that olmesartan could trigger immune-mediated enteropathy, a hypothesis in line with the inhibitory effects of the angiotensin receptor blockers on transforming growth factor beta, an immunoregulatory cytokine necessary for gut immune homeostasis [17]. Interestingly, cases of enteropathy related to other angiotensin II receptor inhibitors seem to be much less frequent than OIE [4]. The selective role of olmesartan might be explained by its conversion into the active form in the intestine, its long half-life and its efficacy, 30 fold higher than that of other sartans.

Altogether these data support caution when using olmesartan in patients with an autoimmune background.

Author Contributions

Conceived and designed the experiments: GM SS NCB CC. Performed the experiments: BM NG NB VV CD EM. Analyzed the data: GM SS BM NCB VV NB. Contributed reagents/materials/analysis tools: GM CC BM NCB VV NB PS GS GC LV LM FC CD EM. Wrote the paper: GM SS NCB. Performed the retrospective analysis of medical files, collected clinical, histological and molecular data: GM SS. Performed histological review of biopsies specimens: VV NB. Performed molecular analysis: CC EM. Provided clinical data: PS GS GC LV LM FC CC. Performed isolation and phenotyping of intestinal lymphocytes: BM NG. Contributed to data analysis: NCB. Reviewed the paper: GM SS BM NG NB VV CD EM PS GS GC LV LM FC NCB CC.

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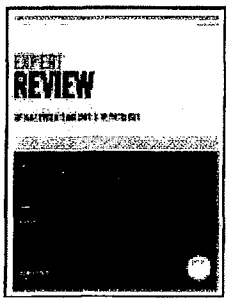

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Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-celiac villous atrophy

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Editorial

Identification of new cases of severe enteropathy has recently increased the spectrum of intestinal non-celiac villous atrophy

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From olmesartan-induced enteropathy to small CD4$^+$ T-cell intestinal lymphoproliferation, the spectrum of non-celiac villous atrophy has recently been largely extended. Precise characterization of the different types of non-celiac enteropathy with villous atrophy is necessary to avoid misdiagnosis, to identify a causal mechanism and propound appropriate therapeutic strategies. This paper discusses how to use the different diagnostic tools to address diagnostic criteria, citing the examples of recent new cases of non-celiac enteropathy with intestinal villous atrophy.

Within the past 20 years, the spectrum of non-celiac enteropathy with villous atrophy has considerably increased. Besides Whipple disease and tropical sprue [1], some entities have been more recently characterized such as adult autoimmune enteropathy [2], or common variable immunodeficiency (CVID) [3]. Expert histopathological analysis with immunohistochemistry is necessary for diagnosis of the precise type of intestinal non-celiac villous atrophy. For example, chorionic plasmocytic rarefaction and nodular lymphoid hyperplasia point out to CVID enteropathy, and the diagnosis can be confirmed by serum protein electrophoresis and anamnesis of frequent upper respiratory tract infections [3]. HLA of type II may also be useful as absence of HLA haplotypes encoding HLA-DQ2 or DQ8 excludes celiac disease as a cause of villous atrophy [4]. Nevertheless, genotypes HLA-DQ2/DQ8 can be found in non-celiac enteropathy such as in patients with CVID bearing celiac susceptibility genotypes in 77% of cases [3]. *In situ* studies of intestinal biopsy can be usefully completed by flow cytometric analysis of intestinal lymphocytes and multiplex PCR detection of T-cell rearrangements [5]. For example, CD4 lymphoproliferations are often misdiagnosed by routine histology and confused with clonal refractory celiac disease due to the combined presence of villous atrophy, decreased frequency of CD8$^+$ intraepithelial lymphocytes (IEL) and presence of intestinal clonal T-cell receptor rearrangement [6,7]. Flow cytometry is very useful to demonstrate that, in contrast with type II refractory celiac disease, counts of CD103$^+$CD3$^-$ IEL are very low, while the frequency of CD103$^-$CD4$^+$ IEL is increased due to diffusion of malignant *lamina propria* CD4$^+$ T cells into the epithelial compartment. Flow cytometric determination of malignant CD4$^+$ T cells is less informative in *lamina propria* that is naturally rich in CD4$^+$ T cells but cytometry may allow identification of the T-cell receptor Vbeta chain used by the clonal malignant CD4$^+$ T cells. Detection of this Vbeta chain is then helpful to monitor diffusion and response to treatment [6,7]. Serology is another complementary diagnostic tool. Anti-transglutaminase antibodies can be

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observed in one-third (5/15) of patients with adult autoimmune enteropathy and thus lack specificity to eliminate celiac disease [2]. In contrast, the presence of serum antibodies against enterocytes or goblet cells is characteristic of autoimmune enteropathy [2]. Serum antibodies can be detected by staining intestinal tissue sections and/or by radioimmunoassay detecting reactivity of anti-enterocyte antibodies reacting with the brush border 75-kDa antigen (AIE-75KD) first described in immune dysregulation, polyendocrinopathy, enteropathy and X-linked (*IPEX*) syndrome [8]. Several rare genetic immune diseases of Mendelian inheritance have recently been identified as a possible cause of autoimmune enteropathy. Most have an early onset in infancy. Yet, some such as cytotoxic T-lymphocyte-associated protein 4 haploinsufficiency and signal transducers and activators of transcription 3 activating mutations can be of incomplete penetrance and develop only at the adult age stressing the need to consider immunological workup and genetic analyses in these patients [9].

Pharmacological drugs such as mycophenolate mofetil may also cause intestinal villous atrophy [10]. The mechanism of its toxicity remains unclear. Recently, a new cause of sprue-like enteropathy has been described in association with use of olmesartan, an angiotensin II receptor antagonist used to treat arterial hypertension. Indeed, several cases of chronic diarrhea with weight loss, anemia and low serum albuminemia have been reported after the use of olmesartan [11]. In 2012, Rubio-Tapia *et al.* reported 22 cases of severe sprue-like enteropathy associated with olmesartan [12]. All patients displayed villous atrophy. Celiac susceptibility genotype HLA-DQ2 was found in around 68% of them, but no serum anti-transglutaminase antibodies were detected and none of the patients responded to a gluten-free diet. Notably, three of them had detectable serum anti-enterocyte antibodies. In another series of 72 patients with unexplained intestinal villous atrophy and negative celiac serology, 16 cases were ascribed to the use of olmesartan [13]. More recently, a French National cohort study reported 36 cases of olmesartan-induced enteropathy, 32/36 of which had villous atrophy but none of them had serum anti-transglutaminase antibodies [14]. In our experience (personal data) [15], olmesartan enteropathy can mimic autoimmune enteropathy. Common histological features were severe villous atrophy with glandular apoptotic lesions. One-third of patients displayed serum anti-AIE-75KD antibodies and, before olmesartan discontinuation, all had responded to immunosuppressive drugs [15]. A recent US study demonstrates that this severe gastrointestinal disorder is in fact a very rare adverse effect of this angiotensin receptor-blocker [16]. It is therefore possible that olmesartan enteropathy only affects predisposed individuals. The pathogenesis of olmesartan-induced enteropathy remains to be elucidated. Since angiotensin receptor blockers can inhibit signals from transforming growth factor beta, a key immunoregulatory cytokine [17], Rubio-Tapia *et al.* have suggested an immune-mediated mechanism. This hypothesis is supported by the increased prevalence of the HLA-DQ2/DQ8 genotype [12,15], the presence of extra-intestinal autoimmune diseases in one-third of our patients and the beneficial effect of immunosuppressive drugs, which sometimes need to be pursued several weeks after olmesartan discontinuation [15].

In conclusion, the use of new diagnostic tools has recently considerably extended the spectrum of non-celiac villous atrophy. Precise characterization of the enteropathy is indispensable to identify the causal mechanism and to propose a pertinent treatment.

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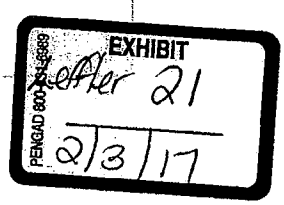

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IL-15: a central regulator of celiac disease immunopathology

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Summary

Interleukin-15 (IL-15) exerts many biological functions essential for the maintenance and function of multiple cell types. Although its expression is tightly regulated, IL-15 upregulation has been reported in many organ-specific autoimmune disorders. In celiac disease, an intestinal inflammatory disorder driven by gluten exposure, the upregulation of IL-15 expression in the intestinal mucosa has become a hallmark of the disease. Interestingly, because it is overexpressed both in the gut epithelium and in the *lamina propria*, IL-15 acts on distinct cell types and impacts distinct immune components and pathways to disrupt intestinal immune homeostasis. In this article, we review our current knowledge of the multifaceted roles of IL-15 with regards to the main immunological processes involved in the pathogenesis of celiac disease.

Keywords

IL-15; celiac disease; tissue; autoimmunity; cytotoxic T cells; loss of oral tolerance

Introduction

Since its discovery in 1994 (1–3), the role of IL-15 has expanded tremendously from a T-cell growth factor to pleiotropic cytokine that acts on virtually each cell type of the innate and adaptive immune system. For a long time, IL-15 was viewed as a cytokine that primarily plays a role in immune homeostasis, namely in NK cell and memory $CD8^+$ T-cell homeostasis. However, the fact that multiple reports depict the overexpression of IL-15 in tissues targeted by autoimmune processes poses the question of whether IL-15 may play a role in tissue immunity and be implicated in the development of organ-specific autoimmune disorders. Celiac disease (CD) is a T-cell-mediated intestinal disorder induced by dietary gluten that is a unique disease model to study the pathogenesis of autoimmune disorders in humans. Since IL-15 was first proposed to play a key role in CD pathogenesis (4–6), numerous studies have confirmed its role in multiple phases of the disease and expanded its impact on multiple cell types and immunological responses. In this review, we discuss the

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role of IL-15 in the pathogenesis of organ-specific autoimmunity using CD as a model, but first we highlight some general key features of IL-15 biology and CD pathogenesis.

Overview of IL-15 biology

IL-15 signaling and expression

IL-15 belongs to the family of Type I cytokines encompassing IL-2, IL-4, IL-7, IL-9, IL-21, and IL-15 (7–9). It shares the γc chain (CD132) of its heterotrimeric receptor with all members of the γc family cytokines (10) and the β chain (IL-2/15Rβ or CD122) with IL-2 (11). The interaction of IL-15 with IL-2/15Rβ chain and γc chain leads to the phosphorylation of Jak1 and Jak3, respectively, and to the activation of STAT5 (12–14). The Jak-STAT signaling pathway supports T-cell and natural killer (NK) cell homeostasis and expansion. In addition, IL-15 triggers other signaling pathways in T lymphocytes by promoting the phosphorylation of the Src family cytoplasmic tyrosine kinases, Lck and Syk (15–17), and by activating the phosphatidylinositol-3-kinase (PI3K), the kinase AKT (18, 19) and the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) (20–23) pathways that lead to mitogenic and anti-apoptotic signals (reviewed in 24). Unlike IL-2, IL-15-driven proliferation of T lymphocytes requires FKBP12 (12-Kda FK506-binding protein)-mediated p70S6 kinase (25). In addition, the recruitment of TRAF2 and Syk to the cytoplasmic tail of IL-15Rα chain has been shown to mediate IL-15 signaling in fibroblasts and neutrophils (26, 27).

IL-15 is a unique cytokine, because it is not secreted and can be upregulated on the surface of all cell types under conditions of inflammation and stress. Its expression on the cell surface requires the 'private' IL-15Rα chain. IL-15 is bound to IL-15Rα intracellularly during synthesis in the endoplasmic reticulum, shuttled to the surface, and is presented in *trans* to responder cells expressing the other IL-15R subunits, IL-15Rβ and γc; thus, IL-15 signaling acts in a cell contact-dependent manner (28–30). IL-15Rα stabilizes binding and greatly enhances the affinity of IL-15 for IL-2Rβ (31). Although IL-15 transpresentation represents the main mechanism by which IL-15 interacts with its receptor *in vivo*, alternative mechanisms have been proposed. For instance, *cis*-presentation represents another mechanism that involves soluble IL-15 binding to IL-15Rα allowing signaling of adjacent IL-2Rβ/γc on the same cell (32–34). Murine and human IL-15 and IL-15Rα can exist not only in membrane bound but also in a soluble form. Thus, the abundance of soluble IL-15Rα/IL-15 complexes that are cleaved from the surface of cells (35–37) suggests that IL-15 complexed to IL-15Rα could also mediate IL-15 responses. Nevertheless, it still remains unclear whether *cis*-presentation or stimulation by soluble IL-15Rα/IL-15 complexes are active mechanisms *in vivo* (38). Expression of IL-15 is tightly regulated at the level of transcription, translation, and intracellular trafficking, avoiding excessive protein production and secretion (39). The translation of IL-15 mRNA into protein is limited by the presence of multiple AUG initiation sites in the 5′-UTR region, a long signal peptide, and a negative regulatory element in the C-terminus of the IL-15 mature protein coding sequence (39, 40). Alternative splicing also controls IL-15 expression. Distinct IL-15 isoforms encoding the same mature protein that use different signal peptides are generated by alternative splicing. These different signal peptides drive the trafficking of IL-15 to distinct

intracellular compartments where IL-15 isoforms are differentially translated (41–45). However, it is unknown whether expression of IL-15 isoforms contributes to tissue-specific regulatory functions. In addition, multiple isoforms of IL-15Rα contribute to IL-15 regulation. Splice variants of IL-15Rα in human monocytes and dendritic cells have been shown to determine the mode of action of IL-15, by either preventing the release of IL-15/IL-15Rα heterodimers from cell membranes thereby favoring transpresentation, or by promoting the release of IL-15 as a soluble secreted cytokine that can act on neighboring cells in a paracrine fashion (46). Therefore, IL-15 expression is fine-tuned at multiple levels to ensure that the cytokine can undertake its numerous functions. The fact that IL-15 acts mostly in a cell contact-dependent manner and that IL-2 preferentially signals via the high affinity IL2Rα-IL2Rβ-γc receptor may explain why these two cytokines that share a common signaling model yet promote different, and even opposing, outcomes. For instance, it is striking to note that inflammation and autoimmunity are associated with IL-2 deficiency (47–50) but that a dysregulated increase in IL-15 expression is observed in many inflammatory autoimmune diseases (51).

Both stromal cells and antigen-presenting cells mediate IL-15 transpresentation depending on the tissue of residence, their location within the tissue, and the responder cell (38). IL-15 expression by both hematopoietic cells and non-hematopoietic cells, i.e. medullary thymic epithelial cells, hepatic stellate cells and bone marrow stromal cells, is involved in the development and survival of naive $CD8^+$ T cells, invariant NKT cells, and NK cells (52–58). Macrophages and dendritic cells are critically involved in IL-15 transpresentation to memory $CD8^+$ T cells, hepatic invariant NKT cells, and differentiated NK cells (35, 52, 59–65). Thus, distinct stages of lymphocyte differentiation require IL-15 transpresentation by different cell types, which include both hematopoietic and non-hematopoietic cells (38).

In the gut, IL-15 expression is influenced by innate immune signaling. Indeed, TLR4 activation was shown to upregulate IL-15 on dendritic cells (35), and intestinal epithelial cells (IECs) require MyD88 for the expression of IL-15 and to promote the maintenance of intraepithelial lymphocytes (IELs) in an IL-15-dependant manner (66). This suggests that the microbiota, in the absence of overt inflammation, could continuously stimulate MyD88 signaling and hence contribute to the constitutive intestinal expression of IL-15 during steady state conditions. Furthermore, it has been suggested that Nod2 signaling might maintain the expression of IL-15 via recognition of the microbiota, as reduced IL-15 expression contributes to the loss of IELs in NOD2-deficient mice (67). Finally, consumption of a diet high in polyunsaturated fat leads to a decrease in IL-15 expression and concomitant reduction in IELs (68). Nevertheless, whether a direct association exists between diet, microbiota, and IL-15 expression has yet to be determined.

Role of IL-15 in immune homeostasis

The critical multifaceted roles of IL-15 during immune homeostasis are well established. IL-15 regulates adaptive memory CD8αβ TCRαβ T cells, as well as innate and innate-like lymphocytes. Its role in B-cell biology under physiological conditions is still under investigation.

Extensive characterization of mice deficient in IL-15 or in its private receptor α chain (IL-15Rα) demonstrated that IL-15 is required for the development, maintenance, and expansion of memory $CD8^+$ T cells (38, 69–76), NK cells (77), and invariant NKT cells (49, 63, 70, 72, 78). IL-15 promotes the survival of $CD8^+$ T cells by increasing the expression of the anti-apoptotic molecule Bcl-2 (79). In addition to its extensive role in promoting cell development and survival, it has been shown that IL-15 induces iNKT and NK cells activation (35, 53, 80–84) and increases the cytotoxicity of NK cells (85).

IELs in the small intestine represent a heterogeneous population of T cells composed mainly of TCRαβ and TCRγδ $CD8^+$ T cells residing within the intestinal epithelium whose main role is to maintain the integrity of the epithelial layer by eliminating infected cells and promoting epithelial repair (86). In mice, IL-15 and IL-15Rα expression on intestinal epithelial cells (IECs) was shown to be critical for the survival and development of innate-like T-cell lymphocytes, i.e. $CD8\alpha\alpha^+$ $TCR\alpha\beta^+$ T cells and $TCR\gamma\delta^+$ T cells (38, 49, 63, 64, 70, 72, 87–89). Furthermore, $TCR\gamma\delta^+$ IELs were also shown to be expanded in transgenic mouse models where IL-15 is overexpressed in IECs (90). The mechanism underlying IL-15-mediated survival of unconventional IELs involves the activation of the Jak3-Jak1-PI3K-Akt-ERK pathway to upregulate Bcl-2 and Mcl-1 (79, 88, 91, 92). Additionally, it has been suggested that IL-15 can regulate the generation of the restricted TCR variable gamma-region gene repertoire of $TCR\gamma\delta^+$ IELs (93), yet the exact role that IL-15 plays on γδ T cells is unclear. IL-15 does not seem to be critical for the survival of $TCR\alpha\beta^+$ $CD8\alpha\beta^+$ T cells whose numbers are maintained in the absence of IL-15Rα (72, 88). The limited expression of IL-2/15Rβ expression on CD8αβ T cells that reside within the intestinal epithelium could provide an explanation as to why IL-15 is less critical for this subset of IELs in mouse (38), yet the signals required for the survival of this subset of IELs remain to be determined. Nevertheless, it was shown that human $CD8\alpha\beta^+$ IELs respond to IL-15 and its presence increases their cytolytic properties (6, 94, 95) and upregulates the expression of NK receptors (5, 6, 96), suggesting that IL-15 may impact on $CD8\alpha\beta^+$ IELs function under inflammatory conditions. Furthermore, it was shown that $TCR\gamma\delta^+$ IELs are expanded in intestinal organ cultures treated with IL-15 (97). IL-15 has also been recently implicated in the activation of human intraepithelial Type 1 innate lymphoid cells by promoting the production of IFN-γ (98). This latter observation is in line with the critical protective role played by IL-15 in defense mechanisms against invading pathogens, especially in the gut (99, 100). Although mice deficient in IL-15 or IL-15Rα exhibit normal numbers of B lymphocytes (70, 72, 101), *in vitro* studies also suggest that IL-15 can modulate B-cell activities by promoting the differentiation and proliferation of activated human B cells as well as immunoglobulin production (102, 103). Finally, besides its wide range of activities on lymphocytes, IL-15 has an impact on dendritic cells, neutrophils, and mast cells by preventing their apoptosis (104–107).

IL-15 overexpression in organ-specific autoimmune disorders other than celiac disease

In accordance with its essential role in regards to the control of immune homeostasis, IL-15 expression is tightly regulated at the translational, transcriptional, and intracellular trafficking levels and coordinated with cellular fate in myeloid vs. lymphoid cells (39, 108). Removal of these control mechanisms results in abnormal IL-15 expression in multiple cell

types, whose 9 detrimental impact is exemplified in many autoimmune disorders and chronic inflammatory diseases. More specifically, IL-15 is upregulated in tissue cells that are targeted by an autoimmune process such as rheumatoid arthritis (109–114), multiple sclerosis (115, 116, 120), psoriatic arthritis or psoriasis (117–119), systemic lupus erythematosus (121–123), and type-1 diabetes (124). Furthermore, increased levels of IL-15 and/or IL-15-IL15Rα complexes have also been documented in the serum of patients with systemic lupus erythematosus (121, 123) or type-1 diabetes (124, 125). There is also dysregulated expression of IL-15 and IL-15Rα in the mucosal tissues of patients with inflammatory bowel disease (IBD) (126–130).

Mechanisms invoked to explain the role of IL-15 in organ-specific autoimmune disorders involve facilitating the maintenance of $CD8^+$ memory T-cell survival including that of self-reactive memory T cells (9, 51), bystander activation with secretion of additional inflammatory cytokines by neighboring cells (51), activation of B cells (129), and upregulation of the activating NK receptor on $CD8^+$ T cells (5, 6, 96, 131) and $CD4^+$ T cells (132, 133).

Overview of celiac disease

CD is an inflammatory disorder with autoimmune features that occurs in genetically susceptible individuals expressing HLA-DQ2 or HLA-DQ8 molecules. CD patients develop inflammatory T-cell and antibody responses against dietary gluten, a protein present in wheat, rye, and barley (134). In addition, CD patients develop autoantibodies specific for the enzyme tissue transglutaminase (TG2). The disease is the 'tip of an iceberg' that includes a much larger undiagnosed population with various aspects of dysregulation of adaptive and innate immunity in response to gluten (135). The typical histopathological picture of CD is a small intestine enteropathy that is characterized by crypt hyperplasia, a massive increase in IELs, and villous atrophy as a consequence of surface IEC destruction. CD can be classified as classical or potential, depending on the presence of histological abnormalities in duodenal biopsies (136). Potential CD is defined by the presence of inflammatory anti-gluten immune response and anti-TG2 antibodies in the absence of villous atrophy, and therefore represents an incomplete, less severe form of CD. In contrast, classical active CD is characterized by the presence of villous atrophy (4, 137, 138), even though the identification of mucosal abnormalities upon intestinal biopsy is no longer required for diagnosis when anti-TG2-antibodies are detected (136). Withdrawal of gluten from the diet is classically associated with normalization of serology and progressive recovery of villous structures (139–143). However, while full recovery tends to occur in children with CD, more than 40% of adult CD patients maintain some level of histological anomalies on a gluten free diet (GFD) (144, 145). Furthermore, despite adherence to GFD, adult CD patients can develop a severe complication called refractory celiac disease (RCD), viewed as an early stage of enteropathy-associated T-cell lymphoma and characterized by severe villous atrophy and the presence of IELs with an abnormal phenotype (146–149).

IL-15 expression in celiac disease

The chronic upregulation of IL-15 in the epithelium (5, 150) and in the intestinal *lamina propria* (LP) (150, 151) is a hallmark of the disease and correlates with the degree of mucosal damage (152). Interestingly, the pattern of IL-15 overexpression differs between potential CD patients, active CD patients, and patients undergoing GFD. While most active CD patients have increased levels of IL-15 both in the intestinal LP and in the epithelium (Fig. 1), IL-15 is not upregulated in IECs in potential CD patients (authors' unpublished data), potentially suggesting that it may be required for development of villous atrophy. Conversely, a high number of CD patients on a GFD maintain high levels of IL-15 expression in the epithelium (Fig. 1), suggesting that dysregulated expression of IL-15 in the epithelium is insufficient to induce villous atrophy. We discuss below, how, according to its location, IL-15 impacts distinct immune components and pathways to disrupt intestinal immune homeostasis.

Role of IL-15 in celiac disease pathogenesis

Because it is upregulated both in the epithelium and in the LP, IL-15 acts on distinct cell types and promotes the dysregulation of multiple immune mechanisms in the small intestine that together contribute to CD pathogenesis (Fig. 2).

Role of IL-15 in loss of oral tolerance

Gluten is a unique protein due to its high content in proline and glutamine residues, and therefore it is a very good substrate for TG2. Prolines prevent gluten from being digested by intestinal enzymes (153), and the presence of a high frequency of glutamines and their spacing with proline (154), make the glutamines within gluten a good target for deamidation by TG2. Hence, the unique amino-acid composition of gluten allows for the generation of long peptides with negative charges that have a relatively high affinity for CD-predisposing HLA-DQ2 (155) and HLA-DQ8 (156), when TG2 is activated (157). However, the generation of peptides able to bind to HLA-DQ2 and HLA-DQ8 does not explain why inflammatory and not regulatory T-cell responses are induced. Indeed, unlike in healthy individuals where regulatory mechanisms allow the intestinal immune response to remain unresponsive to innocuous food antigens [an active process called oral tolerance (158)], CD patients exhibit a loss of oral tolerance manifested by HLA-DQ2 or HLA-DQ8-restricted anti-gluten inflammatory $CD4^+$ T cells secreting interferon-γ (IFN-γ) and IL-21 in the small intestinal mucosa (159–162). Because IL-15 has pro-inflammatory properties and is highly upregulated in the LP of CD patients (150, 151), where dendritic cells taking up dietary antigens reside (163, 164), we hypothesized that IL-15 signaling in dendritic cells may lead to the induction of inflammatory T cell responses against gluten and the loss of oral tolerance (165, 166). Using an HLA-DQ8 mouse model overexpressing IL-15 in the LP but not in the intestinal epithelium, we showed that IL-15 in combination with retinoic acid altered the tolerogenic phenotype of intestinal dendritic cells, hence preventing the generation of inducible $Foxp3^+$ Treg cells to dietary gluten and promoting the development of a T_H1 inflammatory immune response to orally ingested gluten (165). It is important to note, however, that the location of IL-15 overexpression critically determines on which cells it acts and what the pathological impact is. For instance, IL-15 overexpression in the

intestinal epithelium in our hands is not associated with the loss of oral tolerance (165, authors' unpublished data), and potentially explains why ovalbumin-fed mice overexpressing IL-15 in the epithelium but not in the LP show no decrease in Foxp3$^+$ T cells expressing the T-cell-receptor specific for ovalbumin (167). Furthermore, a defect in inducible regulatory T cells can be easily missed if one does not strictly control for TCR specificity using RAG-deficient TCR transgenic T cells (167), because regulatory Foxp3$^+$ T cells without defined specificity are attracted, as are other effector T cells, to inflamed tissues. This explains why Foxp3$^+$ T cells are paradoxically increased in the tissues of autoimmune disorders (168–172) and inflammatory bowel disease (173–179). To which degree Foxp3$^+$ T cells recruited to inflamed tissues encounter their (self) antigen and are activated remains to be determined. Finally, in addition to losing oral tolerance, mice overexpressing IL-15 in the LP produce anti-TG2 IgG and IgA antibodies (165). Interestingly, no villous atrophy was observed in these mice, supporting the concept that in absence of the epithelial stress associated with IL-15 overexpression in the epithelium, adaptive anti-gluten immunity is insufficient to induce tissue damage. Hence, events leading to sustained or repetitive IL-15 upregulation in the LP have the potential to lead to the constitution of a growing inflammatory effector and memory pool of gluten-specific T cells that can result in the development of potential, but not active, CD.

Role of IL-15 in blocking the ability Foxp3$^+$ regulatory T cells to regulate effector T-cell responses

Sallustro and colleagues (180), looking at effector and Foxp3$^+$ T cells in the synovia of juvenile arthritis patients, first proposed that the presence of IL-15 could interfere with the regulatory properties of Foxp3$^+$ T cells. It was later shown that IL-15 blocks the ability of transforming growth factor (TGF-β) to suppress activation of human mucosal T lymphocytes by activating c-Jun N-terminal kinase (JNK) and subsequently impairing Smad-3-dependent TGF-β signaling (181). Disruption of TGF-β signaling likely results in increased proliferation and production of inflammatory cytokines, ultimately promoting sustained intestinal inflammation (152). In addition, by activating the PI3K pathway, IL-15 renders effector CD8$^+$ T cells unresponsive to the suppressive effect of Foxp3$^+$ regulatory T cells (182). This may be by the same mechanism that IL-15 impairs the ability of regulatory T cells isolated from the blood and intestinal biopsies of CD patients to block effector CD4$^+$ T cells *in vitro* (183). Interestingly, while IL-15 alters the response of effector T cells to regulatory T cells, it does not alter the intrinsic regulatory properties of Foxp3$^+$ T cells (184). Altogether, this may explain why despite the increase in Foxp3$^+$ T cells in inflamed tissues of patients with CD, autoimmune disorders, and IBD, effector T cells are highly effective at promoting tissue damage.

Role of IL-15 in the licensing of cytotoxic T cells to kill epithelial cells and induce active celiac disease

The induction of non-classical MHC class I molecules and the upregulation of IL-15 on IECs, as well as the dysregulated activation of IELs that acquire cytotoxic properties, are a hallmark of CD and were shown to be critically involved in the development of villous atrophy. Cytotoxic IELs are not gluten-specific but rather kill epithelial cells based on the recognition of stress signals (4, 6, 166). In healthy individuals, IELs mainly express the

inhibitory CD94/NKG2A receptor (5, 131) and only low levels of the activating NKG2D receptor (6). In contrast, IELs from CD patients lack the inhibitory CD94/NKG2A receptor (185) and express high levels of the activating NKG2D and CD94/NKG2C receptors (96, 185). Concomitantly, IECs in the inflamed mucosa of CD patients express high levels of the stress-inducible MIC molecules (96, 186), and non-classical MHC class I molecule HLA-E (185), which are the main ligands for NKG2D and CD94/NKG2C, respectively. IL-15 was shown to upregulate the activating NKG2D receptor, endowing cytotoxic IELs with the ability to kill IECs expressing the stress-induced MIC molecules (6, 96, 187). IL-15 stimulation induces CD94 expression in IELs by increasing CD94 transcription and its expression on the cell surface (5). However, it does not affect the expression of NKG2A, NKG2C, or DAP12 (5, 185). Moreover, IL-15 induces the expression of NKG2D (6, 96) by increasing NKG2D and DAP10 transcription (96). Furthermore, IL-15 acts as a costimulatory molecule for the NKG2D cytolytic pathway (96, 187), hence endowing IELs with lymphokine-activated killer (LAK) activity (6, 96), i.e. with the capacity to kill in a T-cell receptor (TCR)-independent manner. In addition to its ability to endow IELs with LAK activity, IL-15 lowers the overall activation threshold of IELs (6, 94, 186). This could result in the recognition of low affinity epithelial self-antigens and the ability to kill epithelial cells in absence of cognate antigens but in a TCR-dependent manner. This scenario is supported by studies in mice showing that $CD8^+$ T cells can reject solid tumors expressing IL-15 in a TCR-dependent manner despite the fact that they do not express the cognate antigen for the $CD8^+$ T cells mediating their rejection (188).

In our view, it is very likely that the destruction of epithelial cells by IELs involves both the TCR and NK receptors. Importantly, only epithelial cells expressing IL-15 and ligands for activating NK receptors will be destroyed. Hence, despite the fact that IELs in the presence of IL-15 act as innate-like lymphocytes that kill epithelial cells based on stress signals, this destruction is highly specific. This led us to propose that IELs in CD are autoreactive and that CD is a model for organ specific autoimmunity (189). This concept is further supported by the presence of autoantibodies specific for TG2, which are required for the diagnosis of CD.

Role of IL-15 in promoting survival of abnormal intraepithelial lymphocytes and promoting refractory celiac disease

In the case of RCD, sustained expression of high levels of IL-15 in the epithelium (150, 190) leads to the expansion of a subset of $CD3^-$ cytotoxic IELs that have undergone profound genetic reprogramming of their NK functions, ultimately acquiring an aberrant and highly activated NK cell-like phenotype (148). IL-15 is thought to contribute to the expansion and survival of these IELs with an aberrant phenotype by exerting anti-apoptotic action on IELs (150, 190, 191). Indeed, IL-15 is able to activate an anti-apoptotic cascade, involving phosphorylation of Jak3 and STAT5 and the increased expression of the anti-apoptotic B cell lymphoma-extra large (Bcl-xL) protein (190). In addition to playing a critical role in the sustained survival of these abnormal IELs, IL-15 also increases their cytolytic capacities (186). Refractory sprue is mimicked in an IL-15 transgenic mouse model where human IL-15 is expressed in intestinal epithelial cells. This upregulation of IL-15 is associated with the expansion of activated NK-like cytotoxic IELs and villous atrophy (190, 192). The link

between IL-15, the increase in NK-like cytotoxic IELs and villous atrophy, is supported by the finding that blocking IL-15 signaling prevents villous atrophy (192), suggesting that neutralizing IL-15 or blocking its signaling may be a treatment for RCD.

IL-15 and genetic risk factors of celiac disease

Because of its large contribution to CD immunopathogenesis, one would have expected the identification of *il15* as a CD susceptibility gene by genome wide association studies. However, no genetic association has yet been found for the gene encoding IL-15 (193). This lack of association suggests that the increased levels of IL-15 in patients might be the consequence of the deregulation of genes capable to modulate the levels of the cytokine; that is, *trans* effects. By analyzing the functional interactions among CD susceptibility genes and IL-15, we found that several of the genes were associated with IL-15, suggesting that the increased levels of IL-15 observed in CD patients probably results from functional variation in this CD-susceptibility network (Fig. 3). Interestingly, among the genes that have direct associations with IL-15 in this network are the γc cytokines IL-21 and IL-2, which share many common structural and functional properties with IL-15. More generally, the genes associated with IL-15 are strongly enriched for key pathways that are central for the pathogenesis of CD such as IgA production, T-cell receptor signaling, or antigen processing and presentation. We also observed a significant enrichment for genes belonging to the autoimmune thyroiditis and Type 1 Diabetes pathways, an observation in accordance with several reports showing that IL-15 upregulation is associated with increased risk for such diseases (124, 125, 194, 195).

Functional redundancy between IL-21, type-1 IFN, and IL-15 in celiac disease

Due to shared receptor components and signaling pathways, γc cytokines theoretically present a high degree of redundancy. In fact, IL-15 and IL-21 exert many overlapping activities in regards to CD immunopathogenesis (Fig. 4) including the ability to render effector $CD4^+$ T cells resistant to the suppressive effects of regulatory T cells (196), the ability to drive the production of IFN-γ (160), and the ability to upregulate cytotoxic activity in IELs (197). Although *in vitro* studies have demonstrated that IL-21 by itself has very little effect, if any, on the proliferation of $CD8^+$ T cells, IL-21 synergizes with IL-15 to promote $CD8^+$ T-cell activation and expansion, production of IFN-γ, and upregulation of granzyme B and perforin (198). The fact that IL-15 enhances the production of IL-21 suggests the establishment of an amplification loop that could foster the ongoing inflammatory response (199). In agreement with the hypothesis that IL-21 could contribute to the induction of inflammation and tissue damage in CD is the finding that potential CD patients not only lack IL-15 overexpression in the LP, but also fail to express IL-21 (200). Although they do not share structural components and signaling pathways, Type I interferon (IFN) is another cytokine that could exert redundant effects with IL-15 (Fig. 4). IFN-α expression is dysregulated in the small intestine mucosa of CD patients (201–203). In addition, clinical observations of the development of CD in hepatitis C patients treated with IFN-α (204) as well as the induction of inflammatory anti-gluten responses and the generation of TG2 antibodies following rotavirus infections (205) suggest that IFN-α likely plays a critical role in the induction of inflammatory T-cell responses against gluten. However, whether and how Type I IFN contributes to CD pathogenesis remains to be determined.

Conclusions and future directions

Overall, the involvement of IL-15 in multiple steps of the NKG2D cytolytic pathway, together with its confirmed roles in abrogating oral tolerance to dietary gluten and interfering with the suppressive activity of intestinal regulatory T cells, makes this cytokine a key player involved in the dysregulation of immune responses in CD. Future studies will also better delineate the role of IL-15 in other organ-specific autoimmune disorders. In particular, it will be important to determine whether IL-15 is critical in the development of autoreactive T-cell responses and the destruction of the tissues targeted by the autoimmune process. In this regard, it is interesting to note that LADA (latent autoimmune diabetes in adults) patients, unlike type-1 diabetes patients, lack IL-15 overexpression in islet β-cells (124), suggesting that, as observed in potential CD, upregulation of IL-15 in tissue cells is critical to license cytotoxic T cells to kill the tissue targeted by the autoimmune process.

Although the exact factors and mechanisms responsible for triggering IL-15 upregulation have yet to be defined, it has been suggested that gliadin peptides could promote IL-15 expression by IECs (186, 206). However, this effect is likely indirect, due to the upregulation of multiple inflammatory mediators as a consequence of T-cell activation. Because IL-15 can be induced by many inflammatory stimuli, including cytokines and TLR ligands (207, 208), other factors, notably microbial components that are enriched in the intestinal compartment, could promote sustained IL-15 expression. However, it is important to acknowledge that we know very little about the mechanisms underlying IL-15 dysregulation in CD and when this dysregulation occurs.

Due to the central role of IL-15 in the immunopathogenesis of CD, there is a growing interest in developing novel therapies able to dampen the actions of IL-15. To inhibit IL-15 activity and to prevent its deleterious effect on oral tolerance and IELs activation, several agents have been developed, including antibodies specific for IL-15 or IL-2/15Rβ, and Jak inhibitors. The humanized antibody (Hu-Mik-β-1) directed towards IL-2/15Rβ prevents the transpresentation of IL-15 by antigen-presenting cells to neighboring NK cells and $CD8^+$ T cells (9, 209). The administration of TMβ-1 (the anti-mouse equivalent of Hu-Mik-β-1) to IL-15 transgenic mice results in the abrogation of inflammatory cytokine production and in the reversal of intestinal damages (165, 192). The Food and Drug Administration has authorized the usage of Hu-Mik-β-1 to treat CD patients with the type II form of RCD (210), who develop enteropathy-associated T-cell lymphoma with a two year survival of less than 30% (146, 211). Another approach consists of interfering with the IL-15 signaling pathway. It involves the administration of the Jak2/3 inhibitor tofacitinib that has been shown to completely reverse the intestinal pathological changes observed in the $T3^b$-hIL-15 transgenic mouse model (212). Finally, *ex vivo* experiments have demonstrated the capacity of the humanized anti-IL-15 monoclonal antibody AMG714 to inhibit the activation of Jak3 and STAT5 in the mucosa of type II RCD patients. In addition, the administration of AMG714 to IL-15 transgenic mice restores IELs apoptosis and consequently inhibits their accumulation (190). Thus, these anti-IL-15 therapies represent promising therapeutic approaches, especially for patients with refractory disease. However, because of the potential redundancy with IL-21, type-1 IFN and yet undefined cytokines, we cannot

exclude that combination therapies or therapies targeting common signaling pathways may be necessary to achieve a therapeutic effect.

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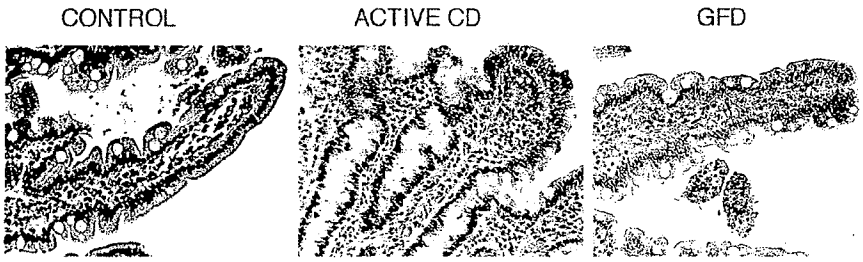

Fig. 1. Patients with active celiac disease have high IL-15 expression both in the intestinal *lamina propria* and epithelium, while patients on a gluten free diet only maintain high expression in the epithelium

Representative pictures of IL-15 immunohistochemistry staining are shown. Duodenal formalin fixed paraffin embedded sections were obtained from control non celiac subjects (control, left panel), untreated (active CD, middle panel), and treated celiac disease patients (GFD, right panel). Epithelial expression was assessed semi-quantitatively looking at staining intensity and localization (typically being stronger at the villous tip and then reducing its intensity going towards the crypts). The rate of IL-15 positive cells on the total number of infiltrating mononuclear cells in the *lamina propria* was assessed by two independent investigators in a double-blind set. Upregulation of IL-15 can be observed in both the small intestinal epithelium and lamina propria of active CD patients. Interestingly, celiac patients on a gluten-free diet (GFD) seem to retain only the epithelial but not the *lamina propria* IL-15 overexpression.

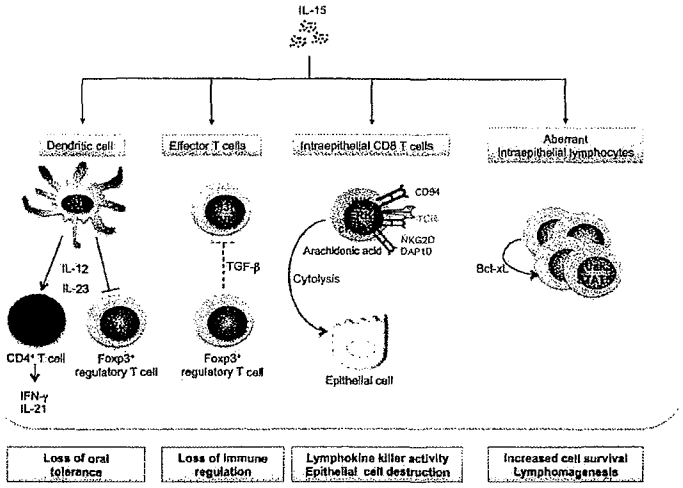

Fig. 2. Multifaceted roles of interleukin-15 (IL-15) in celiac disease pathogenesis

IL-15 impacts distinct cell types to mediate its pathogenic effects. (i) In the *lamina propria*, IL-15 endows mucosal dendritic cells with inflammatory properties in a c-Jun N-terminal kinase (JNK)-dependent manner, and subsequently with the ability to prevent the differentiation of regulatory T cells and to promote inflammatory Th1 cell responses leading to the loss of oral tolerance. (ii) IL-15 renders effector T cells resistant to the suppressive functions of regulatory T cells through a mechanism involving JNK and phosphatidylinositol 3 kinase (PI3K). (iii) IL-15 impacts on intraepithelial lymphocytes by inducing the expression of NKG2D. The synergy between IL-15 and NKG2D cytolytic signaling pathway promotes the binding of the NKG2D-DAP10 complex to distinct adaptor proteins including PI3K whose activation promotes the phosphorylation of the mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (ERK), and JNK. This leads to $cPLA_2$ activation, which in turn critically regulates NKG2D-mediated degranulation and cytolysis, and induces the release of arachidonic acid, a precursor of the pro-inflammatory compounds called leukotrienes. (iv) In patients with refractory sprue, IL-15 leads to the expansion and survival of an abnormal subset of $CD3^-$ intraepithelial lymphocytes by activating an anti-apoptotic cascade involving the phosphorylation of Jak3 and STAT5.

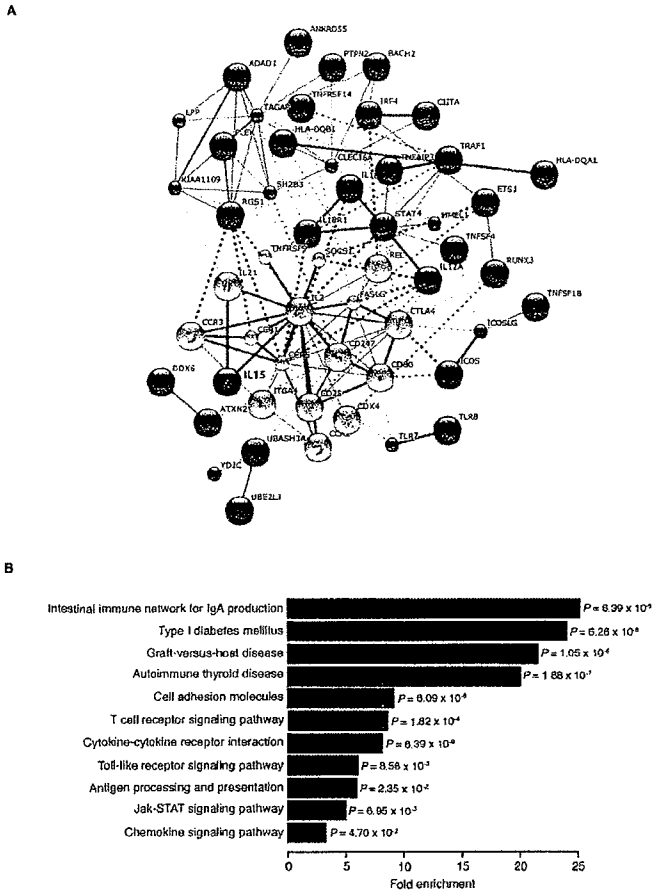

Fig. 3. Interactions between IL-15 and celiac disease susceptibility genes

(A). Network of known interactions between celiac disease (CD)-associated genes and IL-15. We used the STRING database to look for known functional interactions among CD susceptibility genes, as well as functional interactions between CD susceptibility genes and IL-15 (red). The figure only shows CD-associated genes that are directly or indirectly connected with IL-15. STRING database assembles information about both known and predicted protein-protein interactions on the basis of numerous sources, including experimental repositories, computational prediction method, and public text collections. We grouped genes based on the distance matrix obtained from the String global scores. We used the KMEANS algorithm setting the number of groups to three. Proteins pairs with a higher global core (i.e. stronger evidence that they interact together) are grouped together on the same cluster. The three clusters are represented by different colors (yellow, purple, and blue). IL-15 is directly connected with the 'yellow cluster'. The thickness of the lines connecting the genes is proportional to String global scores supporting the evidence of an interaction. Solid and dashed lines represent intra- and inter-cluster connections, respectively. (B). KEGG pathway enrichment analysis for the CD-associated genes shown in panel A. The y-axis reports the fold enrichments observed for genes in a particular pathway (named in y-axis) using all human genes as our background expectation.

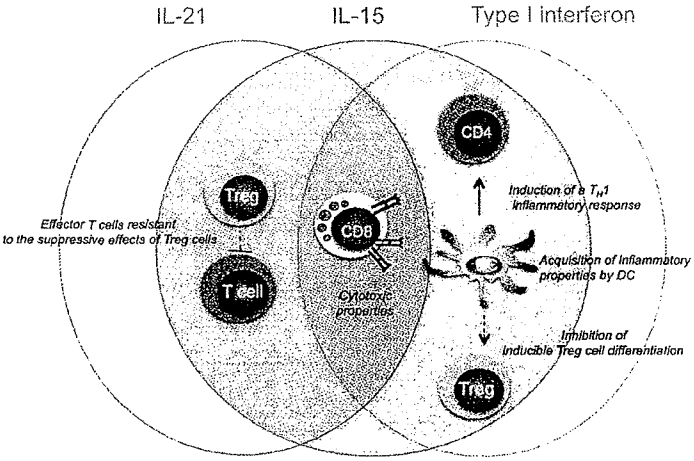

Fig. 4. Overlapping functions of IL-15, IL-21, and Type I interferon

Both IL-15 and IL-21 render effector $CD4^+$ T cells resistant to the suppressive functions of regulatory T cells. Both IL-15 and Type I interferon endow dendritic cells with inflammatory properties and have been shown to mediate loss of oral tolerance and to promote Th1 immunity. All three cytokines have the ability to confer cytotoxic properties to $CD8^+$ T cells.

Exhibit U

Annual Adverse Drug Experience Report: 1996

October 30, 1997

Surveillance and Data Processing Branch
Division of Pharmacovigilance and Epidemiology
Office of Epidemiology and Biostatistics
Center for Drug Evaluation and Research
Food and Drug Administration

TABLE OF CONTENTS

INTRODUCTION

This report presents a descriptive overview of the 159,504 evaluable[1], postmarket adverse drug experience (ADE) cases received by the US Food and Drug Administration (FDA) during calendar year 1996[2]. A case consists of the original report of an ADE on a patient plus any follow-up information.

At this time, October, 1997, the SRS has accumulated about 1.4 million cases. The primary purpose for maintaining the database is to serve as an early warning or signaling system for ADEs not detected during premarket testing. The ADE system depends upon

detection of an adverse clinical event by a health professional or consumer, attribution of the clinical event to prior administration of a particular drug ("suspect" drug), and reporting of the ADE to the manufacturer of the suspected drug or directly to FDA. Data from these ADE cases are coded and entered into the computerized ADE database. Copies of the ADE cases are stored on microfilm or an imaging system. Up to five drugs per case may be entered into the computerized ADE database; the five can be a combination of "suspect" and "concomitant" drugs. Up to four adverse events per case and their associated body systems can by coded into the database, using FDA's "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART).

Reporting of postmarket ADEs by health professionals and consumers is voluntary. They may send their reports directly to FDA ("Direct" reports), to the drug manufacturer ("Manufacturer" reports), or both. Drug manufacturers are required by law and regulation to submit to FDA postmarket ADE reports received by any means from health professional or consumers.

It is important to remember certain caveats when using data from FDA's postmarket ADE database:

1. For any given ADE case, there is no certainty that the suspected drug caused the ADE. This is because physicians and consumers are encouraged to report all suspected ADEs, not just those that are already known to be caused by the drug. The adverse event may have been related to an underlying disease for which the drug was given, to other concomitant drugs, or may have occurred by chance at the same time the suspect drug was administered.
2. Accumulated ADE cases may not be used to calculate incidences or estimates of drug risk. Numbers from these data should be carefully interpreted as reporting rates and not occurrence or incidence rates.

Over the next pages, various kinds of data and information are presented on the postmarket ADE cases computerized into the FDA ADE database during calendar year 1996. Due to rounding, the percentages in tables and graphs may not total to 100%. Figures 1 and 2 present copies of the postmarket ADE forms used by manufacturers and health professionals or consumers, respectively.

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[1] Excludes "React Uneval" unevaluable reactions cases.

[2] The 1996 postmarket ADE Computerized data file used for this report was created October 1997.

Standard MedWatch Form, front page

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: ____ or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defect/malfunction)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____
3. Date of event
4. Date of this report
5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known)
   - -
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date
8. If explanted, give date
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name, address & phone #
   phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

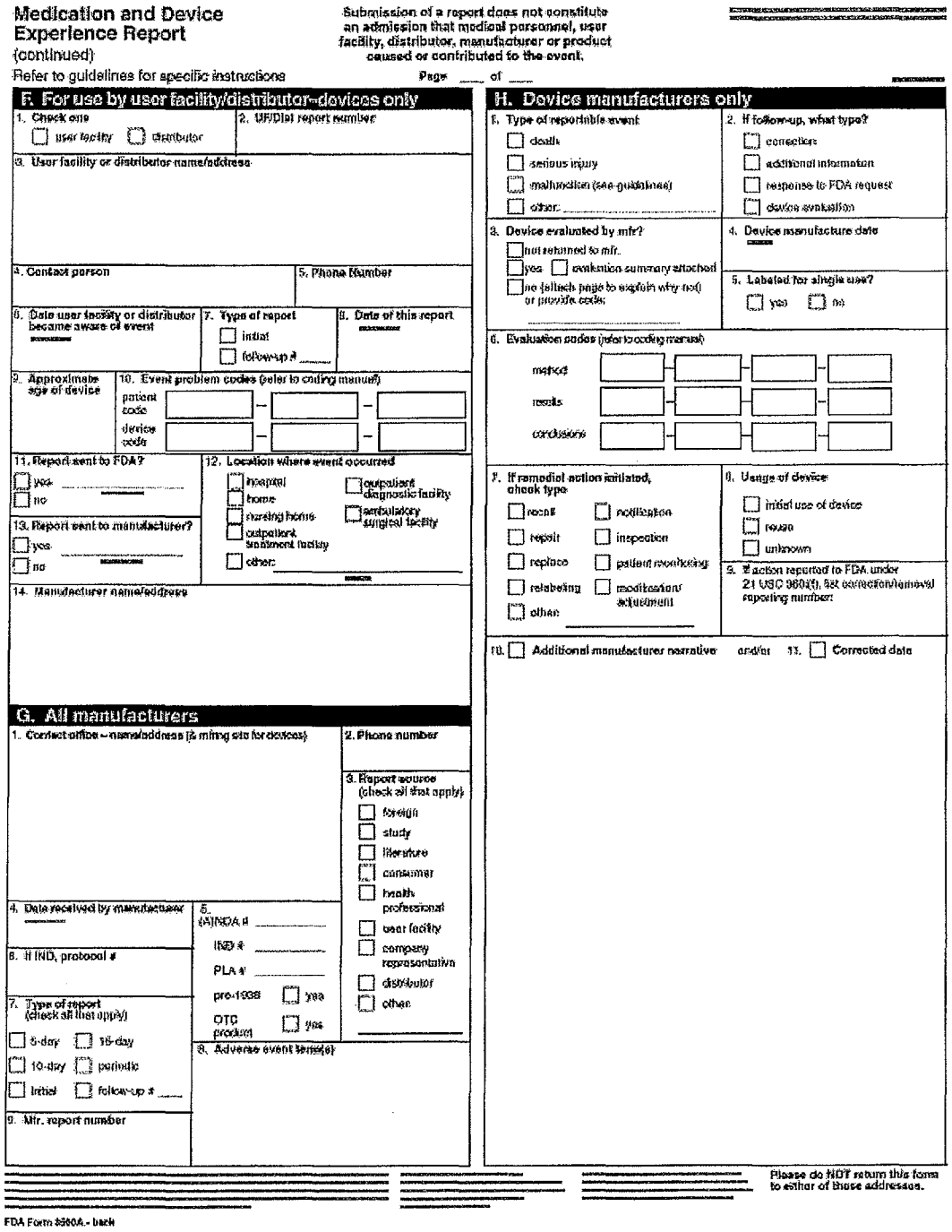
PLEASE TYPE OR USE BLACK INK

FDA

FDA Form 3500A (1/06)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Standard MedWatch Form, back page



Medication and Device Experience Report (continued)

Refer to guidelines for specific instructions

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Page ___ of ___

F. For use by user facility/distributor–devices only

1. Check one: ☐ user facility ☐ distributor
2. MFR/Dist report number
3. User facility or distributor name/address
4. Contact person
5. Phone Number
6. Date user facility or distributor became aware of event
7. Type of report: ☐ initial ☐ follow-up # ___
8. Date of this report
9. Approximate age of device
10. Event problem codes (refer to coding manual): patient code ___ – ___ – ___; device code ___ – ___ – ___
11. Report sent to FDA? ☐ yes ☐ no
12. Location where event occurred: ☐ hospital ☐ outpatient diagnostic facility ☐ home ☐ nursing home ☐ ambulatory surgical facility ☐ outpatient treatment facility ☐ other:
13. Report sent to manufacturer? ☐ yes ☐ no
14. Manufacturer name/address

G. All manufacturers

1. Contact office – name/address (& mfrng site for devices)
2. Phone number
3. Report source (check all that apply): ☐ foreign ☐ study ☐ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other
4. Date received by manufacturer
5. (A) NDA # ___ (B) IND # ___ PLA # ___ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #
7. Type of report (check all that apply): ☐ 5-day ☐ 15-day ☐ 10-day ☐ periodic ☐ initial ☐ follow-up # ___
8. Adverse event term(s)
9. Mfr. report number

H. Device manufacturers only

1. Type of reportable event: ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other: ___
2. If follow-up, what type? ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. Device evaluated by mfr? ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not or provide code: ___)
4. Device manufacture date
5. Labeled for single use? ☐ yes ☐ no
6. Evaluation codes (refer to coding manual): method ___ – ___ – ___ – ___; results ___ – ___ – ___ – ___; conclusions ___ – ___ – ___ – ___
7. If remedial action initiated, check type: ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/ adjustment
8. Usage of device: ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ Additional manufacturer narrative attached 11. ☐ Corrected data

Please do NOT return this form to either of these addresses.

FDA Form 3500A - back

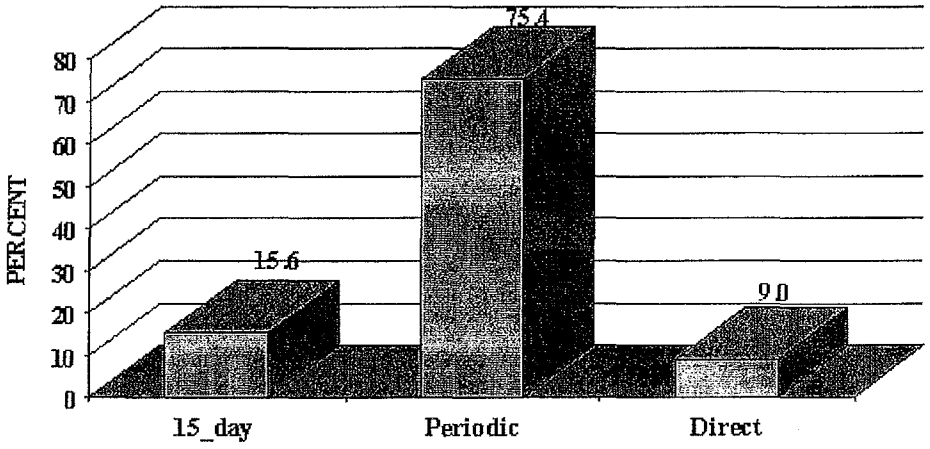
TYPES OF REPORTS

There are three types of reports in the FDA computerized postmarket ADE database:

1. Manufacturer-reported cases concerning ADEs not in present official FDA labeling with serious outcomes (i.e., death, life-threatening, hospitalization, permanent disability, congenital anomaly, cancer, or overdose). These cases are known in regulatory language as "**15-day Alert Reports**" because the manufacturer has 15 working days to submit this type of report to FDA.
2. All other manufacturer-reported cases. These cases are known in regulatory languages as "**Periodic Reports**" because the manufacturer is required to submit them to FDA on a cyclical basis.
3. Cases sent directly to FDA by health professionals or consumers ("**Direct Reports**").

As shown in Figure 3, reports submitted to FDA via manufacturers accounted for 91.0%(145,021) of the 159,504 postmarket ADE cases. Only 9.0%(14,483) were submitted directly to FDA. 15-day report were 15.6%(24,815) of the total.

Figure 3. Postmarket ADE Reports by Type of Report: 1996

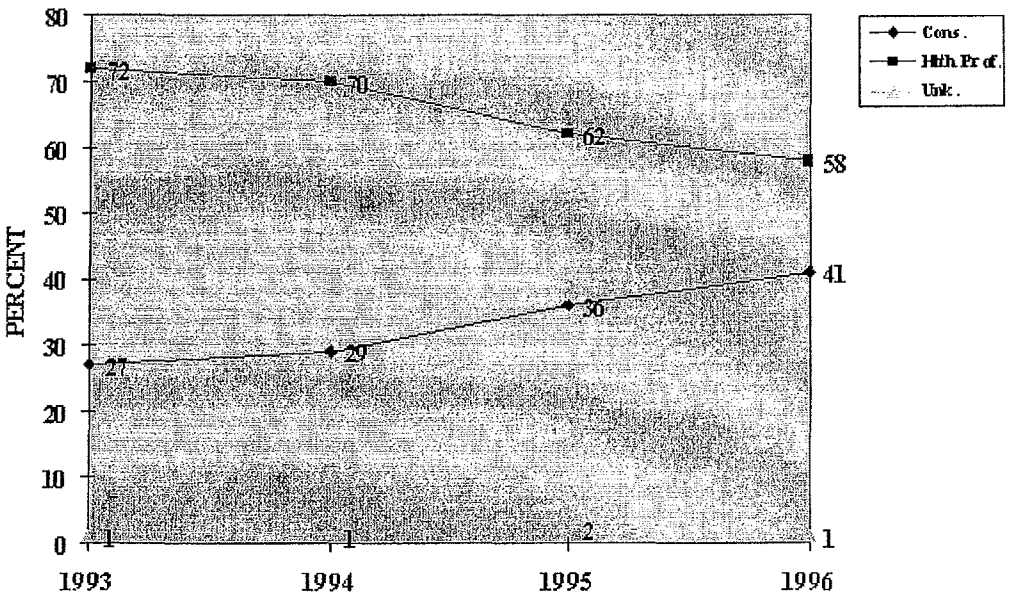


N = 159,504

REPORTING BY HEALTH PROFESSIONALS AND CONSUMERS

As shown in Figure 4, in 1996, there were 157,067 reporters for the 159,504 postmarket ADE cases, 64,752 (41.2%) reporters were consumers, 90,394 (57.6%) reporters were health professionals, and 1,921 (1.2%) were unknown sources. Figure 4 also shows that, over a four-year trend (1993-96), reports from consumers have increased both in absolute numbers and proportionally, whereas those from health professionals have gone up in absolute numbers.

Figure 4. ADE Reports By Health Professionals and Consumers, 1993-1996



Year: 1993 1994 1995 1996

N (000s)			N (000s)			N (000s)			N (000s)		
C	32		C	35		C	48		C	64	
H	86		H	84		H	81		H	90	
U	1		U	1		U	2		U	2	

GEOGRAPHIC LOCATION OF INITIAL REPORTER

As shown in Table 1, the initial reporter for 81.2% (129,521) of the 159,504 postmarket ADE cases was located within the US census regions; 9.6% (15,260) of cases were missing location.

There were 9.2% (14,723) of the postmarket ADE cases where the initial report source was foreign. There were four countries which each accounted for >= 9% of the foreign cases: France (31.2%), Japan (14.2%), United Kingdom (12.8%), Germany (9.2%).

Table 1. Postmarket ADE Reports by Geographic Location of Initial Reporter: 1996

	N	%
All Locations	***159,504***	***100***
US Census Region:	***129,521***	***81.2***
[a] **New England**	25,149	19.4
East South Central	23,355	18.0
Pacific	22,289	17.2
Middle West	22,207	17.2
West South Central	16,804	13.0
Middle Atlantic	16,763	12.9
Others	2,954	2.3
Foreign:	***14,723***	***9.2***
[b] **France**	4,593	31.2
Japan	2,094	14.2

United Kingdom	1,888	12.8
Germany	1,355	9.2
Others	4,793	32.6
Unknown	***15,260***	***9.6***

[a] US Census Regions are percentaged to 129,521
[b] Foreign countries are percentaged to 14,723

SEX AND AGE OF PATIENTS

As shown in Table 2, the ratio of female-to-male postmarket ADE cases was 1.7:1. For both females and males, the >= 60 year age group accounted for the greatest number of known sex-age cases.

Table 2. Postmarket ADE Reports by Reports by Sex & Age of Patient: 1996

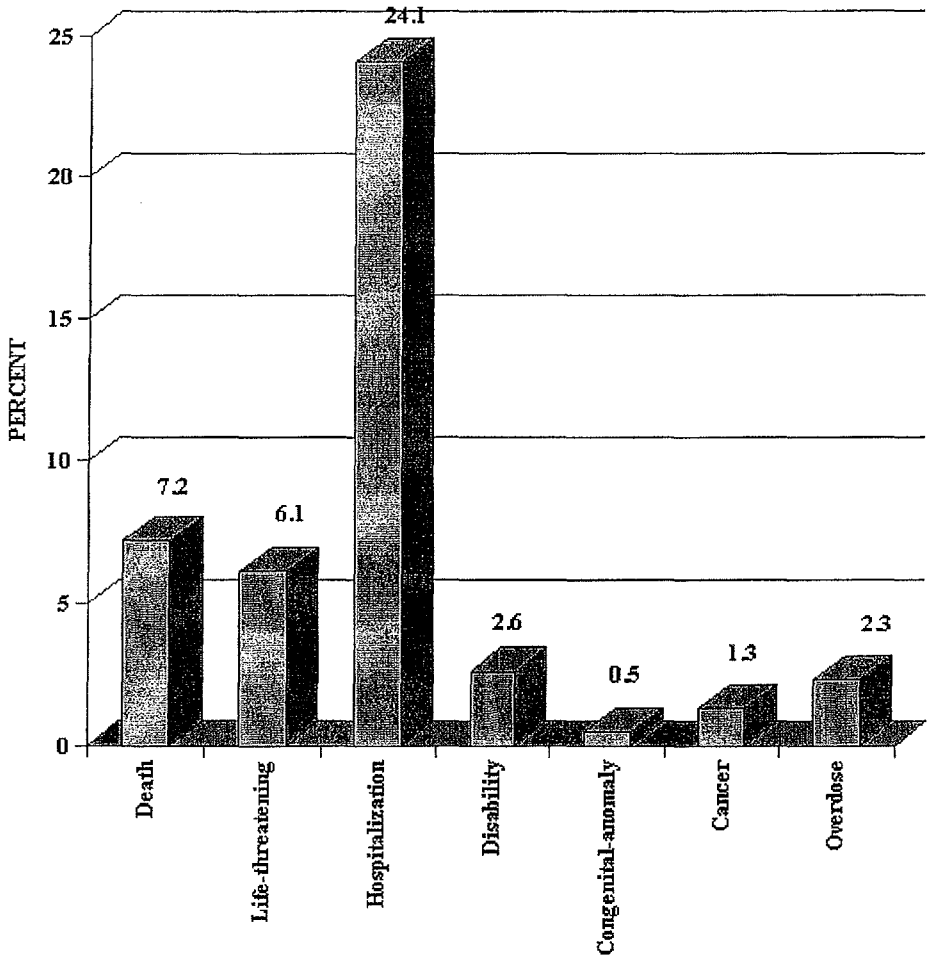
	N	%
ALL SEXES & AGES	***159,504***	***100***
All Females:	***91,200***	***57.2***
<= 19 yrs	5,971	3.7
20 - 39 yrs	19,855	12.4
40 - 59 yrs	20,980	13.2

>= 60 yrs	24,111	15.1
Unknown age	20,283	12.7
All Males:	***53,761***	***33.7***
<= 19 yrs	5,069	3.2
20 - 39 yrs	8,510	5.3
40 - 59 yrs	13,082	8.2
>= 60 yrs	17,418	10.9
Unknown age	9,682	6.1
Unknown Sex:	***14,543***	***9.1***
<= 19 yrs	439	0.3
20 - 39 yrs	163	0.1
40 - 59 yrs	242	0.2
>= 60 yrs	312	0.2
Unknown age	13,387	8.4

SERIOUS OUTCOMES

As shown in Figure 5, hospitalization was the most recorded serious outcome; congenital anomaly, the least. (One case could have more than one outcome).

Figure 5. Postmarket ADE Reports by Type of Serious Report: 1996

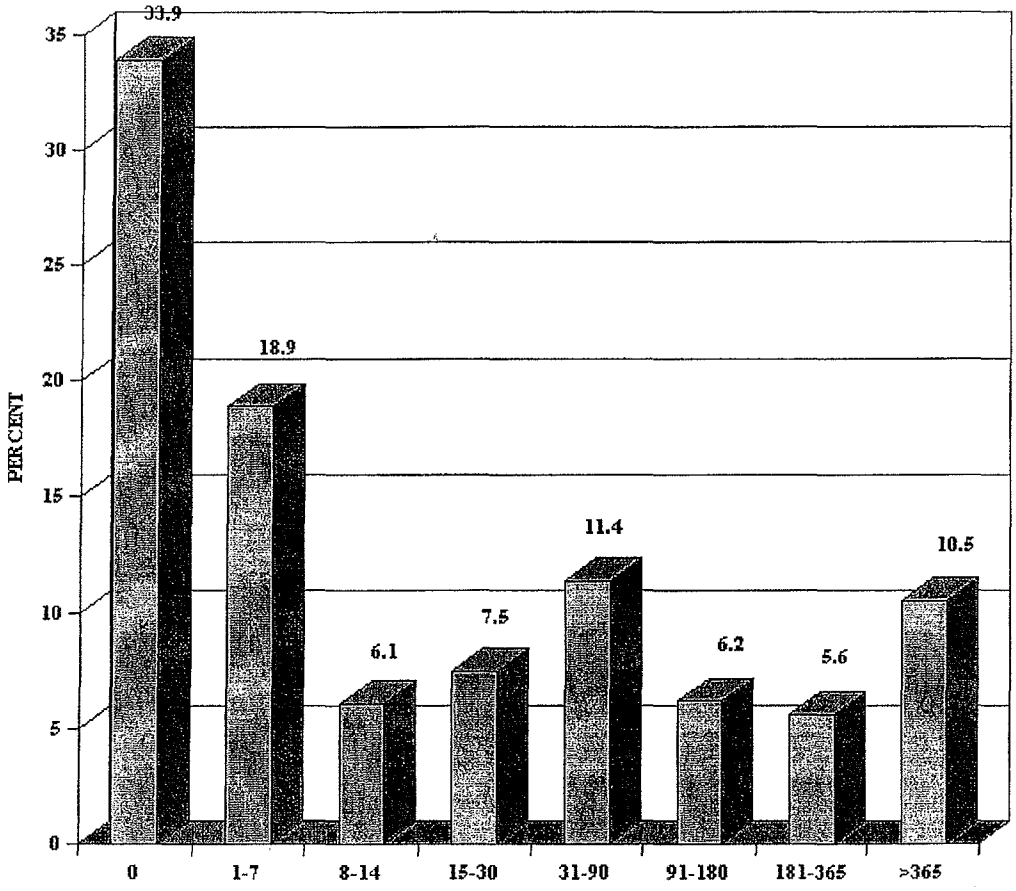


LATENCY BETWEEN SUSPECT DRUG ADMINISTRATION AND ADE ONSET

As shown in Figure 6, of the 159,504 postmarket ADE cases, 53.6% (85,517) had both a drug start date and an adverse experience onset date for the first-listed suspect drug and first-listed adverse experience, respectively, and the drug date was computerized as

occurring before the adverse experience date. About half of these cases noted that the adverse event occurred within one week of drug initiation.

Figure 6. Postmarket ADE Reports by Latency Period: 1996



Latency (days)

N = 85,517

CLASSES OF SUSPECT DRUGS

Table 3 presents the top-10 ranked drug classes associated with the 174,905 suspect drugs computerized from the 159.504 postmarket ADE cases. The top-ranked drug class, central nervous system agents, accounted for approximately little less than one-quarter of

the drug class mentions[3]. Together with the second and third ranked drug classes, anti-infectives, and hormones and synthetic substitutes, these top three ranked drug classes comprised about half of the total drug class mentions.

Table 3. Postmarket ADE Reports by Top-10 Ranked Classes of Suspect Drugs: 1996

	N	%
All Suspect Drug Mentions	***174,905***	***100***
Central nervous system agents	39,541	22.6
Anti-infective agents	21,388	12.2
Hormones & synthetic substitutes	20,956	12.0
Cardiovascular drugs	18,076	10.3
Skin & mucous membrane agents	13,927	7.9
Antineoplastic agents	12,552	7.2
Gastrointestinal drugs	10,580	6.0
Unclassified therapeutic agents	10,397	5.9
Autonomic drugs	8,189	4.7
Blood formation and coagulation	3,707	2.1

[3] The drug classification used was the American Hospital Formulary Service Pharmacologic - Therapeutic Classification (American Society of Health-System Pharmacists, Bethesda, Maryland, 1997)

SUSPECT DRUGS BY ENTRY NAME AND NEW MOLECULAR ENTITY STATUS

Table 4 shows the top-10 ranked suspect drugs as entered on the 159,504 postmarket ADE reporting forms.

New Molecular Entities (NMEs) are defined as new drugs approved within the past three years. For this 1996 report, NMEs are new drugs approved during 1993-96. Of the 174,905 suspect drugs computerized from the 159,504 postmarket ADE cases, 30.2%(29,584) involved NMEs.

Table 4. Postmarket ADE Reports by Top-10 Ranked Suspect Drugs: 1996

	N	%
All Suspect Drug Mentions	***174,905***	***100***
Fosamax™	6,197	3.5
Norplant™	5,957	3.4
Prozac™	3,506	2.0
Pepcid AC™	3,104	1.8
Estraderm™	2,890	1.7
Femstat™	2,648	1.5
Rogaine™	2,435	1.4
Paragard™ T380A	2,172	1.2
Nix™	2,077	1.2
Zoloft™	2,070	1.2

™ - Trademark

DRUG CLASSES STRATIFIED BY HEALTH PROFESSIONALS OR CONSUMERS, TYPE OF REPORT, AND YEAR

Table 5 shows the top-five ranked drug classes[3] associated with suspect drugs, stratified by whether the initial reporter was a health professional or consumer, the type of report, and year the cases was computerized into the FDA postmarket ADE database.

1996 Data. In 1996, there were 155,529 drug class mentions where type of initial reporter and type of report were known. For consumers, only two of the top-five ranked drug classes were common to all report types: central nervous system agents and hormones and synthetic substitutes. For health professionals, there were four drug classes of the top-five ranked drug classes common to all report types: central nervous system agents, antineoplastic agents, anti-infective agents, and cardiovascular drugs. The only drug class in the top-five ranked drug classes common to both consumers and health professionals across report types was central nervous system agents.

Table 5. Top-5 Ranked Drug Classes Per Type of Reporter & Report: 1996

Reporter Type	Report Type	Drug Class	N	%
ALL	*ALL*	*ALL*	*155,529*	*100*
Consumer	*All*	*All*	*64,858*	*41.7*
	Mfr 15-day	*All*	*2,820*	*1.8*
		Central nervous system agents	689	0.4
		Hormones and synthetic substitutes	482	0.3
		Anti-infective agents	309	0.2
		Cardiovascular drugs	271	0.2
		Autonomic drugs	233	0.1

	Mfr Periodic	*All*	*61,225*	*39.4*
		Hormones and synthetic substitutes	11,709	7.5
		Skin and mucous membrane agents	10,612	6.8
		Central nervous system agents	10,073	6.5
		Gastrointestinal drugs	7,080	4.6
		Cardiovascular drugs	5,504	3.5
	Direct	*All*	*813*	*0.5*
		Central nervous system agents	222	0.1
		Skin and mucous membrane agents	132	0.1
		Autonomic drugs	88	0.1
		Anti-infective agents	87	0.1
		Cardiovascular drugs	43	0.0
Health Professional	*All*	*All*	*90,671*	*58.3*
	Mfr 15-day	*All*	*20,200*	*13.0*
		Central nervous system agents	4,264	2.7
		Anti-infective agents	3,851	2.5
		Antineoplastic agents	3,165	2.0
		Cardiovascular drugs	2,582	1.7
		Hormones and synthetic substitutes	1,274	0.8
	Mfr Periodic	*All*	*56,998*	*36.6*

		Central nervous system agents	15,324	9.9
		Anti-infective agents	8,061	5.2
		Cardiovascular drugs	5,953	3.8
		Hormones and synthetic substitutes	5,434	3.5
		Antineoplastic agents	3,962	2.5
	Direct	*All*	*13,473*	*8.7*
		Central nervous system agents	3,713	2.4
		Anti-infective agents	2,477	1.6
		Cardiovascular drugs	1,736	1.1
		Antieoplastic agents	1,398	0.9
		Blood formation and coagulation	919	0.6

ROUTES OF SUSPECT DRUGS

Table 6 presents the top-10 ranked routes of administration associated with the suspect drugs. There were 156,759 routes mentioned in conjunction with the 159,504 postmarket ADE cases. About three-fifths of the route mentions noted the oral route of administration.

Table 6. Postmarket ADE Reports by Top-10 Ranked Routes of Administration of Suspect Drugs: 1996

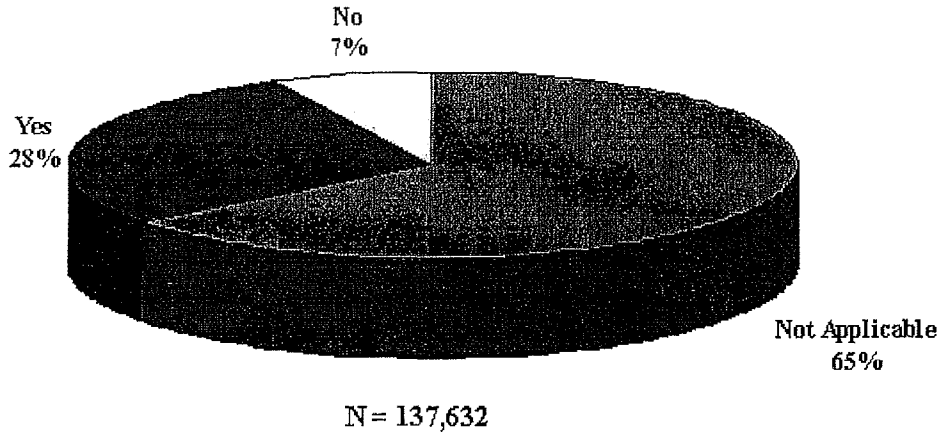
	N	%
All Routes	***156,759***	***100***

Oral	99,421	63.4
Intravenous	14,873	9.5
Subcutaneous	8,204	5.2
Topical	8,181	5.2
Transdermal	7,460	4.8
Vaginal	3,798	2.4
Inhalation	2,739	1.7
Intrauterine	2,318	1.5
Ophthalmic	2,094	1.3
Intramuscular	2,029	1.3

ABATEMENT OF ADVERSE EVENT

For the 174,905 suspect drug mentions, 78.7% (137,632) had an answer to the question of whether the adverse event abated after the suspect drug was stopped or the dose was reduced. Figure 7 shows the distribution of responses. About one-quarter of these 137,632 abate mentions indicated a positive dechallenge ("Yes" response).

Figure 7. Postmarket ADE Reports by Abate response: 1996

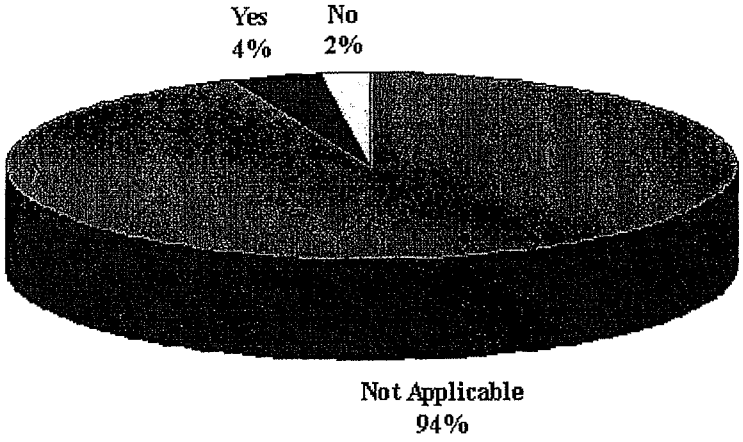


N = 137,632

REOCCURRENCE OF ADVERSE EVENT

For the 174,905 suspect drug mentions, 76.2% (132,296) had an answer to the question of whether the adverse event reappeared after reintroduction of the suspect drug. Figure 8 shows the distribution of responses. Four percent (5,309) of these 132,296 reoccur mentions indicated a positive rechallenge ("Yes" response).

Figure 8. Postmarket ADE Reports by Reintroduction Response: 1996

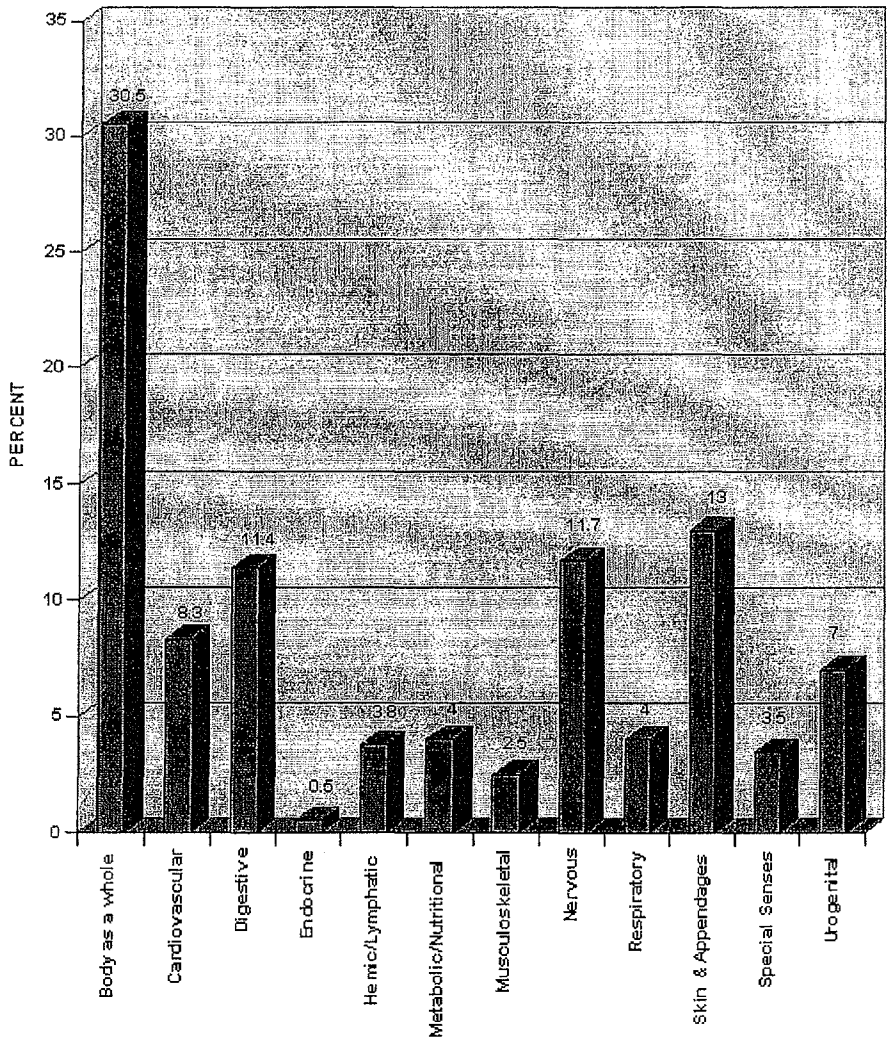


N = 132,296

BODY SYSTEMS

There were 159,515 body system mentions associated with the adverse events of the 159,504 postmarket ADE cases. The distribution of these mentions across the 12 body system mentions is presented in Figure 9. Four body systems each had > 10% of the 159,515 body system mentions: body as a whole (systemic adverse events) - 30.5%, skin and appendages system - 13%, nervous system - 11.7%, and digestive system - 11.4%.

Figure 9. Postmarket ADE Reports by Body System: 1996



N = 159,515

ADVERSE EVENTS

Table 7 shows the top-10 ranked adverse events reported with the 159,504 postmarket ADE cases. The top ranked ADE was " No drug effect: - 10% of the ADE cases reported this event.

Table 7. Top-10 Ranked Adverse Events: 1996

Adverse Event	N	%
All Postmarket ADE Reports	*159,504*	*100*
No drug effect	15,918	10.0
Headache	5,133	3.2
Rash	4,090	2.6
Application site reaction	3,583	2.2
Diarrhea	2,445	1.5
Urticaria	2,373	1.4
Alopecia	2,237	1.4
Aggravation of existing reaction	2,236	1.4
Dizziness	2,002	1.3
Abdominal pain	1,875	1.2

DRUG CLASSES ASSOCIATED WITH BODY SYSTEM ADVERSE EVENTS

Table 8 presents the four body systems comprising the most adverse events, each of which has been crosstabulated by its top-five ranked suspect associated drug classes[3]. Three drug classes were in the top-five ranks for all four body systems, central nervous system agents, cardiovascular drugs, and anti-infective agents.

Table 8. Top-4 Ranked Body Systems with Their Respective Top-5 Ranked Suspect Drug Classes: 1996

Body System	Suspect Drug Class	N	%
Body as a whole	***All***	***53,050***	***100***
	Central nervous system agents	12,131	22.9
	Hormones and synthetic substitutes	7,216	13.6
	Skin and mucous membrane agents	6,378	12.0
	Anti-infective agents	4,816	9.1
	Cardiovascular drugs	4,566	8.6
Skin and Appendages	***All***	***21,792***	***100***
	Hormones and synthetic substitutes	3,948	18.1
	Skin and mucous membrane agents	3,689	16.9
	Anti-infective agents	3,178	14.6
	Central nervous system agents	2,941	13.5
	Cardiovascular drugs	1,931	8.9
Nervous System	***All***	***20,515***	***100***
	Central nervous system agents	8,265	40.3
	Anti-infective agents	2,209	10.8
	Cardiovascular drugs	1,763	8.6
	Hormones and synthetic substitutes	1,463	7.1
	Autonomic drugs	1,425	7.0
Digestive System	***All***	***20,059***	***100***

	Central nervous system agents	4,105	20.5
	Anti-infective agents	4,081	20.3
	Gastrointestinal drugs	2,355	11.7
	Unclassified therapeutic agents	2,256	11.2
	Cardiovascular drugs	1,900	9.5

ANNUAL FOI REPORT

1996

In 1996, the Surveillance and Data Processing Branch (SDPB) received a total of 2,162 Freedom of Information (FOI) requests. These requests were for adverse reaction cases collected by the Food and Drug Administration's Spontaneous Reporting System (SRS). All requests are logged in by the central FOI office and triaged to various responsive divisions throughout the Center for Drugs.

SDPB processed FOI requests utilizing several forms of data accession. Compressed ASCII files were provided to mostly third-party businesses. Microfiche line listings or paper copies were also available depending on the preference of the requester. Case reports from the SRS database were obtained by people wanting a formalized version of the Medwatch form.

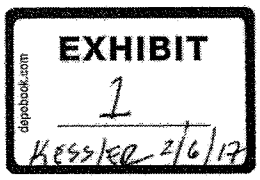
Law firms comprised the most FOI requests, with third-party organizations ranking second. Third were the pharmaceutical companies and last were consumers. However, consumers made more inquiries in 1996 than in previous years. This could have been attributed to media reporting and those consumers wanting to establish a more significant role in their drug therapy.

Hal Stepper

Exhibit V

EXPERT REPORT

DAVID KESSLER, M.D.



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APPENDICES AND SCHEDULES

I. OVERVIEW[1]

1. I have been asked to examine the facts relating to Daiichi Sankyo's Olmesartan[2] and FDA's regulatory process and standards.

2. As part of the process, I examined if, and when, there was a "a reasonable evidence of a causal association, a definitive causal relationship need not be established," for that is the FDA standard for determining whether a company should include a warning in the Warnings and Precautions section of the drug label.

3. I understand that at this juncture of the litigation the Court has ordered the parties to focus on issues of causation.

4. Issues of causality are at the heart of the FDA standard.

5. This report addresses these issues through the prism of FDA's regulatory framework. It addresses if, and when, Daiichi Sankyo should have recognized that there was a reasonable evidence of a causal association between olmesartan and serious gastrointestinal symptoms.

6. The report focuses on the importance of dechallenge and rechallenge data in assessing causal associations under the FDA standard.

7. Simply put, as I describe in more detail below, dechallenge means stopping the drug and seeing if the adverse event goes away. Rechallenge means restarting the drug and seeing if the adverse event comes back. It is a bedrock methodology of establishing a reasonable causal association between a drug and an adverse event.

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[1] For all my opinions, see my full Report.

[2] In this Report, "olmesartan" refers to olmesartan medoxomil and the brand names of the drugs in which it is sold as a monotherapy or combination therapy, including Benicar, Benicar HCT, Azor, and Tribenzor. The labeling history of these drugs is set forth in Schedule IV. All Schedules were prepared by legal staff under my direction and subject to my review.

8. The report shows how FDA has had manufacturers change drug labels based in part on positive dechallenge and rechallenge evidence.

9. The report concludes that by the end of 2006, and certainly by 2007, serious adverse event reports for olmesartan showed reproducible positive rechallenge cases, thus satisfying the FDA standard of "reasonable evidence of a causal association."

10. The report further concludes that despite the fact that there was sound scientific evidence that met the FDA standard by the end of 2006, and certainly by 2007, in Daiichi Sankyo's possession, Daiichi Sankyo failed to act on it and inform doctors and patients.

II. QUALIFICATIONS

11. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978.

12. I did my pediatrics training at John Hopkins Hospital.

13. I was appointed in 1990 by President George H.W. Bush as Commissioner of the United States Food and Drug Administration and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

14. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume is included as Appendix A. A list of cases in which I have appeared as a witness in the last five years and documentation of my expert witness fee is attached as Appendix B. A list of my published articles relating to FDA issues, including drugs and devices, is attached as Appendix C.

15. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act. I was responsible for overseeing five Centers within FDA. They included, among others, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, the FDA announced a number of new programs, including: the regulation of the marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; and the MedWatch program for reporting adverse events and product problems involving both drugs and devices. I created an Office of Criminal Investigation within the Agency.

16. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I served on the board of Aptalis Pharma and serve on the Boards of Stoke Therapeutics, Tokai Pharmaceuticals and the medical device and biologics company Immucor, Inc. In these advisory and fiduciary capacities, I have advised companies on the standards and duties of care within the pharmaceutical and medical device industry. I also chaired the compliance committee of Aptalis, and I chair the quality committee of Immucor, which involves ensuring compliance with FDA laws and requirements.

17. The documents provided to me by counsel, or that I accessed independently from various sources, including, but not limited to, FDA's website, are listed in Appendix D to this report. At my request, Appendix D was prepared by counsel. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

18. In this report I use the term "Daiichi Sankyo" to mean Daiichi Sankyo, Inc.; Daiichi Sankyo U.S. Holdings, Inc.; Daiichi Sankyo Co., Ltd; Forest Laboratories, Inc.; Forest Pharmaceuticals, Inc.; and Forest Research Institute, Inc. I understand that olmesartan was sold as part of a co-promotion agreement with Forest at various points in time.[3]

19. The causes of action in this litigation include: products liability—design defect and failure to warn; gross negligence; negligence; negligence per se; negligent misrepresentation; negligent design; fraudulent concealment; constructive fraud; fraud; breach of express warranties; breach of implied warranties; unjust enrichment; violation of consumer protection laws; loss of consortium; wrongful death; survival action; and punitive damages.

20. The Plaintiffs in the bellwether cases are listed in Schedule IX.

III. THE FDA STANDARD FOR DETERMINING WHETHER THERE IS REASONABLE EVIDENCE OF A CAUSAL ASSOCIATION WITH A DRUG SUCH THAT A COMPANY SHOULD INCLUDE A WARNING IN THE WARNINGS AND PRECAUTIONS SECTION OF THE DRUG LABEL.

21. In 1979, FDA, as part of a final rule titled "Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs" issued 21 CFR §§ 201.57 (e) and (g) which stated, respectively:

> "(e) Warnings: Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved."[4] "(g) Adverse Reactions: An adverse reaction is an undesirable effect reasonably associated with the use of the drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."[5]

[3] See OLM-DSI-0001247338 – 387.

[4] 21 CFR § 201.57(e).

[5] 21 CFR § 201.57(g).

22. In 2006, FDA adopted final rules for 21 CFR §§ 201.57 (c)(6) and (7) which stated:

> "(c)(6) 5 Warnings and precautions. (i) General. This section must describe clinically significant adverse reactions....the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established...." "(c)(7) 6 Adverse reactions. This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event."[6]

23. Hereinafter I refer to post-2006 standard as the "FDA Standard."

IV. REGULATORY OVERVIEW OF OLMESARTAN

24. Benicar, Benicar HCT, Azor and Tribenzor contain the active chemical ingredient known as olmesartan medoxomil. Olmesartan medoxomil is an angiotensin II receptor antagonist used for the treatment of high blood pressure.

25. On April 25, 2002, FDA approved Benicar for treatment of hypertension as a monotherapy containing the active ingredient olmesartan medoxomil (hereinafter "olmesartan"). On June 5, 2003, FDA approved Benicar HCT for treatment of hypertension, as a combination therapy drug containing the active ingredients olmesartan and hydrochlorothiazide. On September 26, 2007, the FDA approved Azor for treatment of hypertension as a combination therapy drug, which contains the active ingredients olmesartan and amlodipine besylate. On

[6] 71 Fed. Reg. 3922-3997 (January 24, 2006) at 3990.

July 23, 2010, the FDA approved Tribenzor for treatment of hypertension as a combination therapy drug, which contains olmesartan, amlodipine and hydrochlorothiazide

26. The original labels for all four drugs did not include any statement in the Warnings and Precautions section of the label regarding olmesartan and serious gastrointestinal symptoms. Listings of gastrointestinal symptoms in Adverse Reactions Clinical Trial Experience and Post-Marketing sections of the labels for the four olmesartan drugs are described in Schedule IV.

27. Daiichi Sankyo submitted an Annual Periodic Adverse Drug Experience Report (PADER) for Benicar to FDA on June 24, 2009, which reported six serious adverse event reports containing the preferred term "coeliac disease."[7] On November 23, 2009, the FDA requested that Daiichi Sankyo provide a review of all celiac disease cases after reviewing Daiichi's PADER.[8] In response to FDA's request, Daiichi Sankyo provided a report on January 14, 2010, identifying 43 reports of adverse events coded with the term "celiac disease" in its global safety database, including 16/17 cases with positive rechallenge.[9]

28. Schedule III provides a timeline of correspondence between Daiichi Sankyo and FDA regarding celiac disease and serious gastrointestinal symptoms involving olmesartan.

29. The FDA also initiated a query using its Mini-Sentinel pilot[10] to assess the risk of celiac disease with the use of angiotensin II receptor blockers, including olmesartan. Mini-Sentinel reports were issued on January 17, 2012 and June 7, 2013.[11]

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[7] OLM-DSI-0001386786

[8] OLM-DSI-0004794456 at 462, 465.

[9] OLM-DSI-0001247409-541, at 419, 423, 425, 432.

[10] "Mini-Sentinel" was a working pilot project of the FDA that uses secure access to the electronic health records of more than 100 million patients with at least 17 data partners. The program was authorized by Congress in 2007. One of the Mini-Sentinel queries that may be

30. On June 29, 2012, the FDA notified Daiichi Sankyo that it had created a Tracked Safety Issue ("TSI")[12] for Olmesartan regarding malabsorption.[13]

31. On July 11, 2012, citing a case series just published by Dr. Murray in the *Mayo Clinic Proceedings* regarding Olmesartan and serious gastrointestinal symptoms, FDA requested that Daiichi Sankyo provide a review of "all serious spontaneous post-marketing reports of malabsorption, enteropathy, microscopic colitis, celiac-like symptoms, or chronic diarrhea with clinically significant weight loss associated with olmesartan," along with any other "additional relevant information on potential underlying mechanism."[14] Daiichi Sankyo submitted a report in response to FDA's inquiry on September 28, 2012, describing a total of 80 adverse event reports which met FDA's criteria in its Daiichi global safety database, including 28 cases with positive rechallenge.[15]

32. The results of FDA's Tracked Safety Issue for olmesartan are documented in a memorandum dated May 14, 2013, which "found sufficient evidence to support an association

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undertaken is to assess potential safety risks with medications. However, the "[d]ata obtained through Mini-Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety." *See* OLM-DSC-0000094055 – 82, at 55; OLM-DSI-0002169412 – 55, at 12.

[11] *See* OLM-DSC-0000094055 – 82; OLM-DSI-0002169412 – 55.

[12] The FDA's Office of New Drug (OND) and Office of Surveillance and Epidemiology (OSE) receive and analyze safety information. When tracking significant safety issues related to marketed prescription and over-the-counter drugs, the FDA may issue a Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) Tracked Safety Issue (TSI). *See* Manual of Policies and Procedures, Center for Drug Evaluation and Research, "Tracking of Significant Safety issues in Marketed Drugs – Use of DARRTS Tracked Safety Issues," effective date of 6/8/2009; 12/20/2011, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM164967.pdf.

[13] OLM-DSI-0002100590-593 at 592.

[14] OLM-DSI-0001247624-626 at 25.

[15] OLM-DSI-0001247542 – 840 at 13-14.

between olmesartan and sprue-like enteropathy," and recommended a revision to the Warnings and Precautions and Adverse Reactions-Postmarketing Experience sections of all labels for Daiichi Sankyo's olmesartan-containing products sold in the United States, and issuance of a Drug Safety Communication to healthcare professionals.[16]

33. On July 3, 2013, the FDA issued a Drug Safety Communication "warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy." The FDA stated that its evaluation "found clear evidence of an association between olmesartan and sprue-like enteropathy," noting that it had identified 10 cases in FAERS[17] of positive rechallenge for "late-onset diarrhea with significant weight loss and, in some cases, with intestinal villous atrophy on biopsy."[18]

V. THE IMPORTANCE OF DE/RECHALLENGE DATA IN ASSESSING CAUSAL ASSOCIATIONS UNDER THE FDA STANDARD.

A. Definition of Positive Dechallenge/Rechallenge

34. "Dechallenge" refers to the withdrawal of a drug from a patient's treatment regime. The FDA defines positive dechallenge as "partial or complete disappearance of an adverse experience after withdrawal of the suspect product." "Rechallenge" refers to the reintroduction of a drug suspected of having caused an adverse experience following a positive dechallenge. The FDA defines positive rechallenge as "reoccurrence of similar signs and

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[16] *See* May 14, 2013, Tracked Safety Issue (TSI) Integrated Review Memorandum, attached hereto in Schedule III.

[17] The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to the FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drugs and therapeutic biologic products.

[18] Caspard Exhibit No. 184.

symptoms upon reintroduction of the suspect product." Dechallenge/rechallenge information is used by the FDA in making causality assessments.[19]

B. The Importance of Dechallenge/Rechallenge Evidence to Assessing Causation Can Be Seen from the Weight that It Is Given in the Medical Literature, by the FDA, and by Daiichi Sankyo.

1. Medical Literature

35. As an example of the importance of how dechallenge/rechallenge data is used in various causation assessment tools, the Bradford Hill criteria, a well-accepted guideline useful for providing evidence of a causal relationship, considers dechallenge/rechallenge evidence. Specifically, the criteria assesses causality from multiple sources using the following parameters: strength of association, temporality (whether condition followed exposure), consistency (reproducibility), specificity (whether there are alternative causes), plausibility (whether the association is biologically plausible), coherence, dose response relationship, experiment **(whether the condition improves upon removal of the hypothesized causative agent),** and analogy.[20]

36. The Naranjo scale is another validated methodology for assessing the causal relationship between a drug and an adverse event using a questionnaire to assign probability scores. Under the scale, the likelihood of whether an adverse event was caused by the drug can be termed "definite," "probable," "possible," or "doubtful." The scoring system gives points for positive dechallenge and positive rechallenge. "A 'definite' reaction was one that (1) followed a

[19] FDA Guidance for Industry, Guideline for Postmarketing Reporting of Adverse Drug Experience (1997), p. 18; *see also* FDA Draft Guidance for Industry. Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (2001), p. 35.

[20] *See e.g.*, Austin Bradford Hill, "The Environment and Disease: Association or Causation," Proceedings of the Royal Society of Medicine, 58 (1965), 295-30; Strom BL, Chapter 3 Basic Principles of Clinical Epidemiology Relevant to Pharmacoepidemiologic Studies, in Strom BL, Pharmacoepidemiology 82-84 (5th ed. 2012).

reasonable temporal sequence after a drug…(2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure."[21]

37. The World Health Organization-Uppsala Monitoring Centre causality assessment recognizes that positive rechallenge information can permit a suspected adverse drug reaction to be upgraded from "probable/likely" to "certain" in its causal connection to the drug.[22]

38. Strom's Pharmacoepidemiology textbook describes the importance of rechallenge data in making causal assessments. "Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment."[23]

39. Another chapter in Strom states that case reports may establish a causal relationship where "there is at least one case with a positive re-challenge and some other supportive cases which do not have known confounding drugs or diseases."[24]

40. A different chapter in Strom states, "[I]t has been suggested that a temporal relationship between medical product and adverse event, coupled with positive de-challenge and

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[21] Naranjo CA, Busto U, Sellers EM, et al., A method for estimating the probability of adverse drug reactions, Clin. Pharmacol. Ther. 30 (2): 239–45 (1981).

[22] Uppsala Monitoring Centre. Pharmacovigilance. Definitions. http://who-umc.org/DynPage.aspx?id=97224&mn1=7347&mn2=7252&mn3=7257 (accessed October 2016).

[23] Strom BL, Chapter 3 Basic Principles of Clinical Epidemiology Relevant to Pharmacoepidemiologic Studies, in Strom BL, Pharmacoepidemiology 86 (5th ed. 2012).

[24] Edwards IR, Olsson S., Lindquist M, Hugman B. Chapter 10 Global Drug Surveillance: The WHO Programme for International Drug Monitoring, in Strom BL, Pharmacoepidemiology 175 (4th ed. 2005).

re-challenge, can occasionally make isolated reports conclusive as to a product-event association."[25]

41. An article in Drug Safety states "[o]nly rarely does the presence of one or more proof positive reports - for instance, in the case of a convincing recurrence on re-exposure to the drug ('positive rechallenge') - produce conclusive evidence with regard to the role of the drug."[26]

42. The Drug Safety article further states "[a] well-documented positive rechallenge, intentional or incidental, may irrefutably prove the connection between a drug and an adverse reaction. Since certainty is notoriously rare in pharmacovigilance, such proof-positive observations (of previously unknown as well as of established adverse reactions) have great scientific value and their reporting is of utmost importance."[27]

2. FDA

43. The FDA gathers dechallenge/rechallenge information in collecting and assessing adverse drug reactions.

44. The FDA's form for reporting adverse drug events, Form 3500/3500A (also known as a MedWatch form), solicits dechallenge/rechallenge data from consumers, health professionals, manufacturers and distributors about the suspect medication. Specifically, the Form asks whether the "event abated after use stopped or dose reduced" and whether the "event reappeared after reintroduction."

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM295636.pdf.

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[25] Rizwanuddin A, Chapter 9 Spontaneous, Reporting in the United States, in Strom BL, Pharmacoepidemiology 152 (4th ed. 2005).

[26] R.H.B. Meyboom, Y.A. Hekster, A.C.G. Egberts, *et al*, Causal or Casual? The Role of Causality Assessment in Pharmacovigilance, Drug Safety 1997 Dec; 17 (6): 374-389 at 377.

[27] R.H.B. Meyboom, Y.A. Hekster, A.C.G. Egberts, et al, Causal or Casual? The Role of Causality Assessment in Pharmacovigilance, Drug Safety 1997 Dec; 17 (6): 374-389 at 383.

45. The FDA's 1997 Guideline for Postmarketing Reporting of Adverse Drug Experiences defines "causality assessment" as including "for example, assessment of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, plausibility, etc."[28]

46. The FDA's guidance for reviewers conducting clinical safety reviews of NDA, stresses the importance of rechallenge information when assessing drug-relatedness of adverse events experienced in clinical trials. "A … reason for individual case review of deaths, serious adverse events, and adverse events leading to discontinuation is to look for results of rechallenge. A potentially important source of information about causality is when an individual is rechallenged with drug, accidentally or deliberately. Recurrence with rechallenge is a potentially strong indicator of causality, but interpretation of the results of rechallenge is highly dependent on the natural course of the event being considered. For noncyclical events that are exceedingly rare in the background (e.g., acute liver failure, aplastic anemia) recurrence of the event upon rechallenge (i.e., positive rechallenge) provides strong evidence of causality. Positive rechallenges are less definitive for diagnoses/events that can occur in cyclical or recurrent fashion (e.g., worsening glucose control in a subject with diabetes mellitus), but close observation of the patient's whole course (i.e., both challenge periods and dechallenge periods) may be helpful."[29]

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[28] FDA Guidance for Industry, Guideline for Postmarketing Reporting of Adverse Drug Experience (1997), p. 18; see also FDA Draft Guidance for Industry. Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (2001), p. 35.

[29] FDA Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, p. 9 (2005).

47. A third FDA Guidance also states, "[i]t is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use."[30]

48. As discussed below, the FDA has required labeling changes based on adverse event reports of positive rechallenge.

3. Daiichi Sankyo

49. Daiichi Sankyo's Standard Operating Procedure ("SOP") for assessing causality of olmesartan serious adverse events in its drug safety database, ARGUS, requires consideration of positive rechallenge information. "A number of factors must be considered when assessing causality, including the study drug (e.g., known pharmacological effect, known adverse event), the patient (e.g., medical history, concomitant medication use), the disease under study (e.g., expected outcome event in the population), the event itself (e.g., whether the event is likely drug induced; specificity of the event), and case-specific information (e.g., plausible temporal association; positive rechallenge)." **A causality assessment of "related" is appropriate "based on a positive rechallenge and lack of other confounding factors."**(Emphasis added.)[31]

50. Daiichi Sankyo's SOP for "Receipt, Assessment, and Reporting of Adverse Events from Non-Study Sources," RM-S01-003 effective April 1, 2007, instructs that causality between an adverse event and drug is "definitely related" if the event: "Follows a reasonable temporal sequence from study product administration; Abates upon discontinuation of the study

[30] FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, p. 4 (2005).

[31] Argus Safety Data Entry Convention, effective March 10, 2014, OLM-DSC-0001431008 at 070.

product (dechallenge); **Is confirmed by reappearance of the reaction on repeat exposure (rechallenge).**" (Emphasis added.)[32]

51. In a September 28, 2012 report to the FDA regarding 80 cases retrieved from the Daiichi Sankyo global safety database reporting malabsorption, enteropathy, microscopic colitis, celiac or sprue like symptoms and chronic diarrhea with clinical significant weight loss, Daiichi Sankyo states that the "most interesting cases" were the reports of positive rechallenges. The report goes on to state that rechallenge is a "rigorous criterion for implicating a drug in drug induced enteropathy."[33]

52. At his deposition on May 6, 2016 Allen Feldman, Daiichi Sankyo's Vice President for Clinical Safety and Pharmacovigilance from 2007 forward, testified as follows:

Q. The third criteria in looking to see if there's a causal relationship is, "Evidence of positive dechallenge or positive rechallenge." You would agree with that, that that's important evidence to look at if you have that information to determine causation?
A. That's very useful information to have.

Q. And again, we went through this earlier in the deposition. A rechallenge is certainly very, very

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important information in terms of determining an association, right?
A. The rechallenge is.[34]

[32] OLM-DSI-0007160734 at 749.

[33] OLM-DSI-0001247542 at 545 and 574.

[34] Deposition of Allen Feldman, May 6, 2016, at 136:14-23 and 230:22-231:3.

C. The Scientific Basis of Rechallenge Testing

53. Using rechallenge methodology experimentally seeks to isolate the role of the drug in contrast to other potential causes/confounding factors. In a rechallenge experiment the variable that is manipulated is the drug. Furthermore, as a positive rechallenge necessarily involves a prior positive dechallenge, there are two experimental instances where the administration or withdrawal of the drug is determined to be linked to the disease. Thus in any positive dechallenge rechallenge situation, there is, in essence, built-in replicability that limits the chances that a confounding factor is at work. As Professor Strom has stated, while there are no guarantees that a positive dechallenge and rechallenge is absolute evidence of causation, practically speaking it is a method of choice for establishing a causal association. FDA regulations require a warning in the Warnings and Precautions section of the label when there is "reasonable evidence of a causal association, a definitive causal relationship need not be established."

54. In my opinion, positive de/rechallenge evidence that is reproducible meets the FDA standard of reasonable evidence of a causal association.[35]

VI. FDA HAS CHANGED DRUG LABELS BASED IN PART ON POSITIVE DECHALLENGE AND RECHALLENGE EVIDENCE

55. My opinion that positive de/rechallenge evidence that is reproducible meets the FDA standard of reasonable evidence of a causal association and can lead to changes in drug labels is further supported by numerous examples of FDA revising drug labels based on de/rechallenge evidence. An analysis of such cases is included in the next section.

[35] Meeting this standard triggers the requirement for a Warning in the Warnings and Precautions section of the label.

A. The Importance of Dechallenge/Rechallenge Data in FDA Drug Safety Determinations Can Be Seen in the Number of Instances Where FDA Used Dechallenge/Rechallenge Data in Making Important Public Health Determinations.

56. I searched for the term rechallenge in FDA Drug Safety Newsletters from Volume 1, November 1 (Fall 2007) to the last available, Volume 2, Number 3 (2009). I also searched FDA Drug Safety Communications from 2010 through 2016 (as of November 27, 2016) and MedWatch Safety Alerts from 2012 through 2016 (as of November 27, 2016). [36]

57. I reviewed FDA Drug Safety Newsletters, FDA Drug Safety Communications, and FDA MedWatch Safety Alerts that resulted in Warnings based on or in part on dechallenge/rechallenge data.

58. This search revealed the following examples of changes in the Warnings based on or in part on de/rechallenge data.

B. Changes to the Warnings & Precautions Section of Label Based on Dechallenge/Rechallenge Data.

59. **Provigil (modafinil).** FDA received six reports of severe skin adverse events, including erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms. According to FDA, "[i]n one case of SJS. . . rechallenge with modafinil resulted in recurrence of the rash. . . which supported a causal relationship with modafinil use." FDA further stated that "[t]he cases described a temporal relationship with detailed clinical descriptions, relevant laboratory data, dermatologist-substantiated diagnoses, skin biopsy confirmation, positive dechallenges, and/or a positive rechallenge, all of which support an association between modafinil use and serious cutaneous

[36] The FDA website for these materials starts at the dates indicated.

skin reactions." The Warnings were changed to add "Serious Rash, Including Stevens-Johnson Syndrome."[37]

60. **Tysabri (natalizumab).** FDA identified in FAERS 28 cases of liver dysfunction, 24 of which were mild lab abnormalities or potentially due to another etiology. FDA stated of the four cases with serious liver injury, "one patient had a positive rechallenge with development of jaundice and significant elevation of liver enzymes after resuming natalizumab." FDA further stated, "[t]he cases. . . describe a temporal relationship between serious liver injury and the use of natalizumab with detailed clinical descriptions, relevant laboratory data, biopsy confirmation of drug-induced liver injury, positive dechallenge, and/or a positive rechallenge. These cases support an association between natalizumab use and serious liver injury." Warnings and Precautions were revised to add: "Hepatotoxicity. Clinically significant liver injury has been reported in patients treated with Tysabri in the postmarketing setting…In some patients, liver injury recurred upon rechallenge, providing evidence that Tysabri caused the injury."[38]

61. **Strattera (atomoxetine).** A search of FAERS and published literature was performed for cases of serious liver injury. In 2004, a labeling change was prompted by two published reports of atomoxetine-induced hepatitis. In one of these reports, there was a positive rechallenge with atomoxetine. As a result, "'[s]evere liver injury. . . postmarketing report. . . of two cases of markedly elevated hepatic enzymes and bilirubin. . . In one patient, liver injury. . . recurred upon rechallenge, and was followed by recovery upon drug discontinuation providing evidence that Strattera caused the liver injury" was added to the Warnings in 2004. Warnings and Precautions were again revised in 2007. Since 2004, FDA received six additional reports of serious liver injury, including two in the published literature. Four of the six patients recovered

[37] Fall 2007 Drug Safety Newsletter; 10/24/2007 Safety Alert.

[38] Spring 2008 Drug Safety Newsletter; 1/2008 Tysabri label.

upon discontinuation of atomoxetine. FDA encourages physicians to inform patients of the signs and symptoms of liver injury and "discontinue and not resume atomoxetine treatment if patients present with jaundice or laboratory evidence of liver injury."[39]

62. **Byetta (exenatide).** FDA reviewed 30 reports of acute pancreatitis associated with use of the drug. In 22 of the 30 cases, a positive dechallenge was reported; three of these cases reported recurrence of various symptoms (e.g., nausea and vomiting, abdominal pain) at re-initiation of exenatide. The FDA also noted that 27 cases reported one or more possible contributory factors, including concomitant use of medications that list pancreatitis among reported adverse events in product labeling, or confounding conditions. Nevertheless, the FDA concluded "[t]hese findings suggested a strong temporal association between exenatide and acute pancreatitis." The product labeling was updated to include information about acute pancreatitis in the Precautions section of the label, and information for healthcare professionals was posted on FDA's website, including a recommendation not to resume treatment "if pancreatitis is confirmed and an alternative etiology for pancreatitis has not been identified." [40]

63. **Viagra and Revatio (PDE5 Inhibitors), Levitra (vardenafil hydrochloride), and Cialis (tadalafil).** A published case report of sudden sensorineural hearing loss (SSHL) in a male patient taking Viagra prompted FDA to search FAERS for postmarketing reports of hearing impairment associated with use of PDE5 inhibitors. There were 29 unique cases describing hearing loss that met the definition of SSHL and "reported a strong or reasonably plausible temporal relationship" with the use of a PDE5 inhibitor, vardenafil hydrochloride, and tadalafil. Two patients reported a positive rechallenge. The FDA revised the labeling for the entire class of drugs to reflect this information in the Adverse Reactions section and provide guidance for

[39] 2009 Drug Safety Newsletter; Volume 2, No. 1, 10/2006 Strattera Label.

[40] Winter 2008 Drug Safety Newsletter, Volume 1, No. 2; 11/01/2006 Label, 1/11/2008 Label.

patients who experience sudden hearing loss in the Precautions, Information for Patients section of the labeling.[41]

64. **Rocephin (Intravenous Ceftriaxone).** FDA reviewed seven case reports from FAERS of serious cardiopulmonary adverse events in neonates undergoing concurrent treatment with Rocephin and calcium-containing intravenous products. Three representative cases were described in detail, including one with a positive rechallenge. A repeat cardiopulmonary event occurred after the second dose. The Warnings were revised to reflect this risk, including that "Rocephin must not be administered simultaneously with calcium-containing IV solutions. . . ."[42]

65. **Cubicin (daptomycin).** FDA located in FAERS and the medical literature seven cases of eosinophilic pneumonia. Two of the cases reported recurrence of eosinophilic pneumonia after Cubicin was restarted. The Warnings and Precautions section of the label was revised to add: "Eosinophilic pneumonia has been reported in patients receiving CUBICIN.... Recurrence of eosinophilic pneumonia upon re-exposure has been reported."[43]

66. **Lamictal (lamotrigine).** FDA reviewed adverse event reports submitted to the Agency for cases of aseptic meningitis. FDA identified 40 cases. Fifteen of the cases reported a rapid return of symptoms following re-initiation of Lamictal. FDA stated, "[i]n these rechallenge cases, symptoms were frequently more severe after re-exposure." The Warnings and Precautions were revised to add: "Aseptic meningitis. Re-exposure resulted in rapid return of

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[41] Winter 2008 Drug Safety Newsletter, Volume 1, No. 2; 2/25/2008 Viagra Label, 12/18/2007 Revatio Label; 10/18/2007 Levitra Label, 10/18/2007 Cialis Label.

[42] 2009 FDA Drug Safety Newsletter, Volume 1, No. 3; 7/17/2007 Label.

[43] 7/29/10 Drug Safety Communication; 11/2010 Cubicin Label.

symptoms (from within 30 minutes to 1 day following re-initiation of treatment) that were frequently more severe." [44]

67. **Proton Pump Inhibitor (PPI) Drugs.** FDA searched FAERS, the medical literature, and periodic safety update reports for reports of low magnesium levels. A total of 38 AERS cases and 23 cases from the literature were found, including eight reported in both FAERS and the literature. FDA stated, "[h]ypomagnesemia has been reported in adult patients taking PPIs for at least three months, but most cases occurred after a year of treatment. . . Some cases cited both positive dechallenge as well as positive rechallenge. . . After restarting the PPI, the median time to develop hypomagnesemia again was two weeks." The Warnings and Precautions Section was revised to add "Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months...treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI."[45]

68. **Saphris (asenapine maleate).** FDA performed a search of FAERS for reports of type 1 hypersensitivity reactions and identified 52 cases. FDA found that "[o]f the 52 cases, 15 reported a resolution of symptoms following Saphris discontinuation, while two of these cases reported a reappearance of symptoms upon reintroduction of Saphris." The Warnings and Precautions Section was revised to add: "Hypersensitivity Reactions, including anaphylaxis and angioedema, have been observed..." [46]

69. **Tumor Necrosis Factor-alpha blockers (Remicade, Enbrel, Humira, Cimzia, Simponi).** FDA performed a search of FAERS and the medical literature for reports of opportunistic pathogens seen in patients treated with TNF-a blockers. FDA identified 80 cases

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[44] 8/12/10 Drug Safety Communication; 10/12/2010 Lamictal Label.

[45] 3/22/11 Drug Safety Communication, 05/2011 label.

[46] 9/1/2011 Drug Safety Communication, 08/2011 label.

of *Legionella* in FAERS and 23 cases in the literature. One published case reported that a "patient developed a second episode of Legionella pneumonia following re-initiation of a TNF-a blocker." The Boxed Warning Section was revised to add the following italicized words: "Bacterial, viral and other infections due to opportunistic pathogens, *including Legionella and Listeria*." [47]

70. **Acetaminophen and acetaminophen-containing medications.** A search of FAERS and the medical literature was performed for serious skin reactions. Three cases of positive rechallenge were found in the published literature. "The evidence supporting causality between acetaminophen and serious skin reactions primarily comes from a small number of published cases in which patients were rechallenged with acetaminophen and had a recurrence of serious skin reaction." The Warnings were revised to add "Serious skin reactions. . . Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity." For over the counter medications, FDA requested/encouraged additional language.[48]

71. **Geodon (ziprasidone).** FDA searched the FAERS database for cases of serious skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Six cases of DRESS associated with ziprasidone use were located. The FDA found that "[i]n three cases, a recurrence of symptoms was reported following the discontinuation and re-initiation of ziprasidone, with a faster time to onset following the re-initiation." The FDA concluded that the "FAERS cases support an association between ziprasidone and the development of DRESS because of the consistency of the case characteristics to the signs and symptoms of DRESS, the

[47] 9/7/2011 Drug Safety Communication; 09/2011 Remicade Label, 12/2012 Enbrel Label, 12/2011 Humira Label, 04/2012 Cimzia Label, 12/2011 Simponi Label.

[48] 8/1/2013 Drug Safety Communication.

temporal relationship between ziprasidone initiation and the onset of symptoms, and reported cases of positive re-challenge." The Warnings and Precautions were revised to add "[d]rug Reaction with Eosinophilia and Systemic Symptoms (DRESS). . . Discontinue ziprasidone if DRESS is suspected."[49]

72. **DPP-4 inhibitors (Januvia, Onglyza, Tradjenta).** FDA searched FAERS and the medical literature for reports of severe, disabling joint pain. The FDA identified 33 cases of severe arthralgia in FAERS. The FDA reported that "[e]ight of the 33 cases documented a positive rechallenge." The Warnings and Precautions were revised to add the following language: ". . . postmarketing reports of severe and disabling arthralgia…A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP4 inhibitor."[50]

73. **Harvoni (ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) and amiodarone in combination with another Direct Acting Antiviral drug.** FDA searched the FAERS database for reports of serious slowing of heart rate. The FDA located nine cases of symptomatic bradycardia. The FDA noted that "[i]n 3 of the patients, rechallenge with hepatitis C treatment in the setting of continued amiodarone therapy resulted in recurrence of symptomatic bradycardia." The Warnings and Precautions were revised to add "Serious Symptomatic Bradycardia When Coadministered with Amiodarone."[51]

74. **Zyprexa.** FDA performed a search of the FAERS database and located 23 cases of Drug Reaction with Eosinophilia and Systemic Symptoms ("DRESS"). FDA noted that "[o]ne reported the recurrence of DRESS after olanzapine was restarted. Nine cases reported the

[49] 12/11/14 Drug Safety Communication; 12/2014 label.

[50] 8/28/15 Drug Safety Communication; 8/2015 labels.

[51] 3/24/15 Drug Safety Communication; 03/2015 labels.

symptoms completely resolved after discontinuation of olanzapine." The Warnings and Precautions Section was revised to add a warning about DRESS.[52]

75. **Abilify.** FDA searched the FAERS database and the medical literature to locate cases of impulse-control problems. The FDA located 184 total cases, 167 in FAERS and 17 in the medical literature. The FDA noted that for the "17 cases published in the medical literature, all cases contained information that the compulsive behavior resolved completely when aripiprazole was discontinued, and four cases reported the return of compulsive behaviors when aripiprazole was restarted." The Warnings and Precautions Section added new warnings about the different types of compulsive behaviors that might result, including the language "consider dose reduction or stopping the medication if a patient develops such urges."[53]

76. Thus, based on the above, from 2007 to present, there were 17 cases where rechallenge data led to a change in the Warnings section of the label in drugs other than olmesartan medoxomil. In 16 of these cases the number of rechallenge cases that led to the change in the Warnings section were specified. In these 16 cases, the average number of rechallenge cases was 3.19, with a range of 1 to 15 and a median of 2.

VII. BY THE END OF 2006, AND NO LATER THAN 2007, SERIOUS ADVERSE EVENT REPORTS FOR OLMESARTAN SHOW REPRODUCIBLE POSITIVE RECHALLENGE CASES, THUS SATISFYING THE FDA STANDARD OF REASONABLE EVIDENCE OF A CAUSAL ASSOCIATION.[54]

77. Daiichi Sankyo's production of MedWatch reports regarding olmesartan, and their corresponding source files, for the ten year period starting at the time of NDA approval (from 2002 through 2012) were reviewed for evidence of serious rechallenge cases involving

[52] 5/10/16 Drug Safety Communication; Zyprexa label.

[53] 5/3/16 Drug Safety Communication; 8/2016 label.

[54] Hereinafter, the term "rechallenge" is used to encompass positive dechallenge and positive rechallenge occurring together.

olmesartan and symptoms of olmesartan associated enteropathy. Any serious reports with a positive rechallenge and symptoms (terms) of diarrhea, vomiting, and/or celiac disease were identified.

78. The methodological review identified 62 MedWatch forms that were submitted to FDA concerning olmesartan and that met the following criteria: 1) at least one of the symptoms of diarrhea, vomiting, or celiac disease appeared in either coded preferred terms in Section G.8 or the narrative in Section B.5; 2) positive rechallenge was documented either through checked rechallenge box in Section C.5 or the narrative in Section B.5; and 3) seriousness was documented either through checked box in Section B.2 or other evidence of hospitalization. I reviewed each of these 62 MedWatch forms, which are attached in Schedule X. These MedWatch forms were produced by Daiichi Sankyo as part of the MDL concerning olmesartan. They were selected from a total of approximately of 9,540 MedWatch reports concerning olmesartan that were produced.

79. Although I am a licensed medical physician, when confronted by a specific medical question, it has been my practice at times, like many physicians, to consult with other medical experts who have considerable expertise in the issue. Toward that end, on November 1, 2016, I wrote to Dr. Daniel Leffler, Associate Professor of Medicine (Gastroenterology) at Harvard Medical School and Director of Research at the Celiac Center at Beth Israel Deaconess Medical Center in Boston, who has published extensively on gastrointestinal symptoms, including celiac disease, and has treated patients with olmesartan associated enteropathy.

80. In my letter of November 1, 2016, to Dr. Leffler, I requested that he review the 62 FDA MedWatch forms and provide his clinical opinion on whether the presentation of symptoms in each of the MedWatch patients after taking olmesartan is consistent with the clinical syndrome

of olmesartan associated enteropathy. I also requested that he exclude any of the 62 MedWatch patients whose presentation of symptoms he believes is inconsistent with the clinical syndrome of olmesartan associated enteropathy.

81. Of the 62 cases submitted to Dr. Leffler, Dr. Leffler concluded that 60 were highly consistent with olmesartan associated enteropathy, both by clinical syndrome and response to olmesartan withdrawal and rechallenge. One of the 62 cases, DSJ-2012-13566, was excluded by Dr. Leffler because the clinical syndrome of constipation, intestinal obstruction and pancreatitis was inconsistent with olmesartan associated enteropathy. A second case, DSM-2011-00109, was excluded by Dr. Leffler because the very fast onset of symptoms, within one week of starting olmesartan, is unusual with olmesartan associated enteropathy.[55]

82. Dr. Leffler also confirmed that the criteria used to identify the MedWatch reports selected—serious positive rechallenges involving diarrhea, vomiting or celiac disease—are highly relevant to clinical diagnosis of olmesartan associated enteropathy.[56]

83. The following chart lists the 60 MedWatch forms that concerned olmesartan, met the three criteria above, and were validated as consistent with the clinical syndrome of olmesartan associated enteropathy.

[55] Expert Report of Daniel Leffler, M.D.

[56] *Id.*

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
1	SU-2004-002638	Diarrhea (narrative) Vomiting	58	F	Box checked	Hospitalization (source file)	Over one year (source file)
2	SU-2005-004027	Vomiting Dehydration Fall Laceration Nausea Hypotension	58	F	Box checked	Hospitalization.	Two years
3	SU-2006-005321	Diarrhea GI inflammation Hypotension	67	M	Box checked	Hospitalization	One year
4	SP-2006-003299	Diarrhea Vomiting Abdominal pain	73	F	Box checked	Hospitalization	Three months
5	SU-2006-005596	CD Diarrhea Vomiting Weight loss Dehydration Anemia Malaise	76	M	Narrative	Hospitalization	Two to three years
6	SU-2006-005527	Diarrhea Vomiting Tropical sprue Weight decreased Renal failure	61	M	Narrative	Hospitalization	Two years
7	SU-2006-005001	CD Vomiting Pyrexia Chills Nausea Diarrhea (narrative)	63	M	Box checked	Hospitalization	Two to three years
8	SP-2006-	Gastroenteritis Hypokalaemia	56	F	Narrative	Hospitalization	Nine months

[57] For the sake of completeness, this includes all coded preferred terms, not only the terms searched for. All terms are coded except where indicated, when term was used in narrative.

[58] From Section C.5 on Medwatch unless other source indicated.

[59] From Section B.2 on the Medwatch unless other source indicated.

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
	003369	Hypocalcaemia Diarrhea (narrative) Vomiting (narrative)					
9	DSU-2007-00076	Vomiting Hypotension Renal failure	unk	M	Box checked	Hospitalization	Unknown
10	DSU-2007-00519	CD Diarrhea Vomiting Hypotension Stress	77	F	Box checked	Hospitalization	Five to six years
11	SU-2007-005968	Diarrhea Weight loss Dehydration	67	M	Box checked	Other Serious	Nine months
12	DSJ-2007-05652	Vomiting Nausea Alanine aminotransferase abnormal Aspartate aminotransferase abnormal Jaundice	70	F	Box checked	Hospitalization	Nine months
13	DSM-2008-00111	Diarrhea Vomiting	59	M	Box checked	Hospitalization	Two years and 7 months
14	DSM-2008-00300	Diarrhea Vomiting	75	F	Box checked	Hospitalization	One year
15	DSM-2008-00239	Vomiting Syncope Loss of consciousness Diarrhea (narrative)	81	F	Box checked	Hospitalization	Eleven months
16	DSU-2008-02107	Diarrhea Vomiting CD Dehydration Weight loss Hypotension	63	M	Box checked	Hospitalization Other Serious	Two years

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
		Nausea Fall Drug administration error					
17	**DSM-2008-00607**	Vomiting Dizziness Tongue disorder	82	F	Box checked	Other Serious	Fifty-six days
18	**DSU-2008-01355**	Vomiting Viral infection Acute kidney injury Sneezing Asthenia Blood pressure increased	70	F	Box checked	Hospitalization	Over one year (narrative)
19	**DSU-2008-02020**	Vomiting Hyponatremia Surgery Blood creatinine increased Glomerular filtration rate decreased Gamma-glutamyltransferase increased Blood cholesterol increased Blood triglycerides increased Blood glucose increased Blood urea increased Blood uric acid increased Blood alkanine phosphatase increased Alanine aminotransferase increased Protein total increased Blood albumin increased	47	F	Box checked	Other Serious	Unknown

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
		Blood cholesterol decreased					
20	DSM-2009-00482	Diarrhea Vomiting Nausea Dehydration Decreased appetite Acute kidney injury Urinary tract infection	81	F	Box checked	Hospitalization Other Serious	One year nine months
21	DSM-2009-00694	Diarrhea Gastroenteritis Hypokalaemia Weight decreased	70	F	Box checked	Other Serious	One year
22	DSM-2009-01869	Colitis Diarrhea (narrative)	83	F	Narrative	Hospitalization Other Serious	Unknown
23	DSU-2009-01835	Diarrhea Vomiting Lipase increased Weight decreased Dehydration	55	F	Box checked	Hospitalization	One year one month
24	DSM-2009-00451	Diarrhea haemorrhagic Vomiting Hypotension	62	F	Box checked	Hospitalization	Unknown
25	DSU-2009-00162	Celiac disease Diarrhea Retching Dehydration Pain Asthenia Renal impairment Hypotension Fatigue Hyperhidrosis	63	M	Box checked	Hospitalization	Four years ago (narrative)
26	DSU-2009-00531	Celiac disease Diarrhea Dehydration Weight decreased Malnutrition Lethargy Blood chloride	65	M	Box checked	Hospitalization Other Serious	Unknown

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
		increased White blood cell count decreased Platelet count decreased Anemia Skin atrophy Confusion Heart rate decreased Hypertension Transferrin saturation increased					
27	**DSU-2009-01026**	Celiac disease Diarrhea Vomiting Cold sweat Dehydration	75	F	Box checked	Hospitalization	Two years
28	**DSU-2009-01282**	Celiac disease	Unk	F	Narrative	Other Serious	Two to six months
29	**DSU-2009-01963**	Diarrhea Vomiting Weight decreased Renal impairment Fall Confusion Asthenia	75	F	Narrative	Hospitalization	One year seven months
30	**DSU-2009-02204**	Celiac disease Diarrhea Vomiting Dehydration Enterocolitis bacterial Hypotension Nausea	62	F	Box checked	Hospitalization	Five years
31	**DSU-2009-02266**	Celiac disease Vomiting Cholecystectomy Malaise Blood pressure increased	69	F	Narrative	Hospitalization Other Serious	One year
32	**DSM-2009-**	Gastroenteritis Acute kidney	63	F	Box checked	Hospitalization Disability or	Three years

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
	00204	injury Diarrhea (narrative)				Permanent Damage	
33	DSU-2010-04766	Celiac disease	65	F	Narrative	Hospitalization	Two years
34	DSU-2010-01914	Celiac disease	66	F	Box checked	Hospitalization	One month
35	DSM-2010-01260	Diarrhea Vomiting	Unk	M	Box checked	Hospitalization	Unknown
36	DSU-2010-00207	Celiac disease Diarrhea Vomiting Weight decreased Gastrointestinal infection Blood pressure increased	76	F	Box checked	Hospitalization Other Serious	Over one year (narrative)
37	DSU-2010-04862	Celiac disease	70	F	Narrative	Hospitalization	Two years
38	DSM-2010-01269	Malabsorption Diarrhea (narrative) Vomiting (narrative)	Unk	M	Narrative	Hospitalization Other Serious	Four years
39	DSU-2010-01718	Diarrhea Hospitalization	> 65	F	Box checked	Hospitalization	Unknown
40	DSU-2010-02706	Vomiting Nausea Gallbladder disorder	70	F	Box checked	Hospitalization	Five years
41	DSU-2010-03745	Vomiting Nausea Hepatic enzyme increased Faeces discolored	63	M	Box checked	Other Serious	Five years
42	DSM-	Diarrhea	73	F	Narrative	Hospitalization	Two years

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
	2011-00236	Vomiting Dehydration Hypokalaemia					seven months
43	**DSM-2011-00846**	Diarrhea Vomiting Abdominal pain Hypotension	76	F	Box checked	Hospitalization	Four hundred and 44 days
44	**DSU-2011-01068**	Coeliac disease	74	F	Box checked	Hospitalization	Unknown
45	**DSU-2011-01739**	Coeliac disease	68	F	Narrative	Other serious	Two to three years
46	**DSM-2011-01329**	Diarrhea Vomiting Weight decreased Abdominal pain	63	M	Box checked	Hospitalization	Two months
47	**DSU-2012-01841**	Diarrhoea Vomiting Nausea Dehydration	67	M	Narrative	Hospitalization Other Serious	Two years
48	**DSU-2012-05283**	Coeliac disease Hip fracture Weight decreased Hypotension	71	F	Box checked	Hospitalization Other Serious	Unknown
49	**DSU-2012-05368**	Malabsorption (SLE) Diarrhea Vomiting	70	M	Box checked	Hospitalization	Months
50	**DSU-2012-05969**	Coeliac disease Vomiting Clostridium difficile infection Hyperhidrosis	72	M	Narrative	Hospitalization	Over one year
51	**DSU-2012-07932**	Diarrhea Intestinal villi atrophy Abdominal pain Nausea Weight decrease Afib Lymphocytic	80	F	Narrative	Hospitalization Other Serious	Over six years

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
		infiltration Gastrooesophageal reflux disease Lab test abnormal (autoimmune test positive)					
52	DSU-2012-09190	Coeliac disease Diarrhea Dehydration Malnutrition Hypotension	87	F	Narrative	Hospitalization	Over three years
53	DSM-2012-00455	Diarrhea Vomiting Dehydration Microcytic anaemia Acute kidney injury	63	F	Box checked	Hospitalization	Two years
54	DSM-2012-00571	Diarrhea Renal failure	80s	M	Box checked	Hospitalization	Many months
55	DSM-2012-00581	Diarrhea Renal failure	55	M	Box checked	Hospitalization	Two years
56	DSM-2012-01055	Diarrhea Vomiting Dehydration Nausea Afib Hypokalemia	69	M	Box checked	Hospitalization Other Serious	Four years
57	DSU-2012-07482	Diarrhea Vomiting Intestinal villi atrophy Gastritis Duodenitis Acute kidney injury Dehydration Syncope Bradycardia Cold sweat Dizziness Nausea Blood pressure	62	M	Box checked	Hospitalization Other Serious	20-24 months

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
		decreased Cardiomegaly Pericardial effusion Emphysema Arteriosclerosis coronary artery Weight decreased Anxiety Fatigue Hepatic steatosis Lipase increased Large intestine polyp Decreased appetite Pyrexia Hiatus hernia Goitre Benign neoplasm of thyroid gland Atelectasis Red blood count decreased Haemoglobin decreased Haematocrit decreased Haemorrhoids Pulmonary mass Blood pressure increased White blood cell count increased Neutrophil count increased Blood magnesium decreased					
58	DSU-2012-08571	Diarrhea Acute kidney injury	56	F	Box checked	Hospitalization	Unknown
59	DSU-2012-09732	Malabsorption (SLE) Diarrhea Vomiting Intestinal villi atrophy Fall Clostridium difficile infection Weight decreased	75	F	Box checked	Life-threatening Hospitalization Other Serious	One year

#	MFR	TERMS[57]	AGE	GENDER	RECHALLENGE[58]	SERIOUS[59]	TIME TO ONSET OF SYMPTOMS
		Dehydration Acute kidney injury WBC increased Blood pressure increased Culture urine positive Hypotension Nausea					
60	DSU-2012-02939	Diarrhea Vomiting Weight decrease Hypotension Clostridium difficile infection Helicobacter infection	81	M	Box checked	Other Serious	Three years

84. A breakdown by year reveals the number of verified positive rechallenge cases with olmesartan to be:

Year	No. of Verified Positive Rechallenge Cases
2004:	1
2005:	1
2006:	6
2007:	4
2008:	7
2009:	13
2010:	9
2011:	5
2012:	14
TOTAL	**60**

85. In my opinion, by the end of 2006, and certainly no later than 2007, there was reproducible positive de/rechallenge evidence that met the FDA standard of reasonable evidence of a causal association.[60]

VIII. DAIICHI SANKYO CONCLUDED THAT ITS SAFETY DATABASE DID NOT SHOW A CAUSAL ASSOCIATION. A REASONABLE AND PRUDENT MANUFACTURER SHOULD HAVE CONCLUDED THAT THE SAFETY DATABASE DID SHOW A CAUSAL ASSOCIATION.

86. Daiichi Sankyo reported to FDA in 2010 and 2012 that its safety database did not show a causal association between olmesartan and enteropathy.[61]

87. Daiichi Sankyo did identify in its reports to FDA 16 positive rechallenges as of December 8, 2009 and 28 positive rechallenges as of July 12, 2012.[62]

88. In fact, as noted above, there were 32 serious positive rechallenges involving diarrhea, vomiting, or celiac disease, as of those December 8, 2009 in Daiichi Sankyo's database, and 53 such positive rechallenges as of July 12, 2012 in its database.

89. In my opinion, a reasonable and prudent manufacturer would have noted and acted upon the reproducible positive rechallenge data in Daiichi Sankyo's database.

90. In my opinion, a reasonable and prudent manufacturer should look for safety problems at all stages of drug development.

91. Herve Caspard, Daiichi Sankyo's Senior Director for Risk Management from 2009 to 2010 provided the following testimony at his deposition on April 7, 2016 .

19 Q. The drug and its label is -- are the

[60] The standard that I have adopted is that positive de/rechallenge evidence that is reproducible meets the FDA Standard for reasonable evidence of a causal association. By 2005, de/rechallenge evidence of olmesartan associated enteropathy had been duplicated, which is the hallmark of reproducibility. By the end of 2006, there were an additional six cases with positive de/rechallenge, which again strengthens a finding of reproducibility.

[61] *See* OLM-DSC-0001556439 – 461 (2010) and OLM-DSI-0001247542 -7840 (2012).

[62] *Id.*

drug manufacturer's responsibility, correct?
A. Yes.
Q. Okay. And regardless of what the FDA requests or not, it is the responsibility, the duty of the drug company, to engage in the drug

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safety analysis throughout the life of the drug. We talked about that earlier, correct?
A. Yes, with respect to the guidance, yes.
Q. Right. So as you're looking at something, and I think what we talked about in good pharmacological practices was that you have to be active. I think I asked you about that.
A. Yeah.
Q. You have to be proactive, right?
THE WITNESS: Yes.
Q. You don't want to be passive and just see what happens, correct?
A. Completely.[63]

92. Tina Ho, Daiichi Sankyo's Executive Director for Clinical Safety and Pharmacovigilance from 2009 to 2015 and previously Senior Director of Risk management from 2006-2009, testified similarly at her deposition on March 23, 2016.

Q. So your company needs to be very vigilant in monitoring adverse events from whatever sources you can --
A. Yes.
Q. -- and to actively seek those out to constantly be assessing the overall safety profile of the drug; correct?
A. Yes.[64]

93. Ms. Ho further testified:

Q. And it talks about the fact -- I think we talked about this earlier -- it's impossible to identify all safety concerns during clinical trials. That's

[63] Deposition of Herve Caspard, April 7, 2016, at 67:19 - 68:15.

[64] Deposition of Tina Ho, March 23, 2016 at 185:4-12.

20 why it's, they say, critical to look at
21 postmarketing safety data after the
22 product is on the market. Right?
23 A. Yes. [65]

94. Similarly, the webpage for Daiichi Sankyo's Quality and Safety Management Unit states that one function it focuses on is "[a]ssurance of patient safety through safety measures based on analyses and evaluations of information on adverse drug reactions received from all stages of use ranging from clinical trials to post-marketing."[66]

95. In my opinion, Daiichi Sankyo failed to adequately identify the safety problems associated with olmesartan associated enteropathy in a timely manner.

IX. DESPITE THE FACT THAT THERE WAS SOUND SCIENTIFIC EVIDENCE THAT MET THE FDA STANDARD IN DAIICHI SANKYO'S POSSESSION BY THE END OF 2006, AND CERTAINLY BY 2007, DAIICHI SANKYO FAILED TO ACT ON IT AND INFORM DOCTORS AND PATIENTS.

96. As discussed above, a reasonable and prudent manufacturer, looking at the de/rechallenge data in Daiichi Sankyo's possession, would have found multiple positive de/rechallenge cases by 2006/2007 and acted upon it.

97. In my opinion, a pharmaceutical manufacturer has an affirmative responsibility to look for and detect serious adverse reactions that can be associated with their drug.

98. In addition, several times over the years the possibility of a safety risk with olmesartan and gastrointestinal symptoms was brought to Daiichi Sankyo's attention.

99. First and most importantly, as noted above, by 2006/2007 Daiichi Sankyo had in their possession multiple MedWatch forms to the FDA that noted positive rechallenges.

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[65] *Id.* at 314:16-23 (referring to Exhibit 111, FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005)).

[66] http://www.daiichisankyo.com/about_us/responsibility/csr/enterprise/reliability/index.html

100. Despite having multiple such reports, there is no evidence that Daiichi Sankyo did any further scientific analysis with this data until November 2009.

101. Second, in November 2009, Daiichi Sankyo's pharmacovigilance consultant Dr. Ronke Dosunmu did an analysis of Daiichi Sankyo's adverse event data and identified five positive dechallenge/rechallenge cases for new diagnoses of celiac disease dating back to 2006.[67]

102. Dr. Dosunmu recommended "further investigation into the clinical database as well as epidemiologic studies be considered to fully understand the issue and determine inclusion into the core data sheet."[68]

103. Based on my search, the record does not show any response to Dr. Dosunmu's recommendations.

104. Third, Dr. Joseph Murray of the Mayo Clinic contacted Daiichi Sankyo in May 2009 and asked the following question: "Do you have any information on GI side effects and Benicar? I am specifically interested in any data pertaining to colitis, enteritis, or sprue-like symptoms."[69]

105. Daiichi Sankyo responded by leaving a message with Dr. Murray's receptionist.[70]

106. Based on my search, there is no record that Daiichi Sankyo provided "any data pertaining to colitis, enteritis, or sprue-like symptoms" to Dr. Murray in response to his inquiry.

107. Dr. Murray contacted Daiichi Sankyo again in November 2010 and January 2011.[71] Daiichi Sankyo submitted a MedWatch form to the FDA describing these additional contacts.[72]

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[67] *See* OLM-DSI-0001401249 – 253.

[68] *See* OLM-DSI-0001401249 at 253.

[69] *See* OLM-DSI-0003380866 – 871, at 866.

[70] *Id.*

108. Dr. Murray initially left a voicemail, on November 26, 2010, stating that he "wanted 'to discuss possible side effects of olmesartan, specifically Benicar and the association with unusual and rare enteropathy (malabsorption). [He] may have seen several cases that would suggest association with this and the use of olmesartan'."[73]

109. On January 26, 2011, Dr. Murray provided additional information in a faxed letter to Daiichi Sankyo, including that "five patients experienced enteropathy-like disease while taking olmesartan medoxomil."[74]

110. Dr. Murray also stated in the letter "I think it may be worthwhile to arrange a time for a telephone call to discuss findings."[75]

111. I can find no record or testimony to indicate that there was any follow up by Daiichi Sankyo with Dr. Murray to discuss his findings prior to the publication of his case series in July 2012.

112. In July 2012, Dr. Murray published the first case series on the association between olmesartan and enteropathy. His paper described 22 patients, seen from August 2008 to August 2011, who experienced chronic diarrhea, weight loss and enteropathy while on olmesartan. Celiac disease was ruled out in all cases. All patients had resolution of their symptoms upon discontinuation of olmesartan. The paper reports that no deliberate rechallenge

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[71] *See* OLM-DSI-0003380866 – 871.

[72] *See* OLM-DSI-0001096152-R – 153-R.

[73] *Id.*

[74] *See* OLM-DSI-0021819177 – 195, at 181.

[75] *Id.*

was undertaken because of the "life threatening nature of the syndrome," but that "2 patients reported anecdotally that their symptoms had worsened when they restarted olmesartan."[76]

113. Fourth, in December 2009, the company undertook a proportional reporting ratio (PRR) of celiac disease cases in FAERS from the first quarter of 2005 to the second quarter of 2009, which revealed a proportionate reporting ratio (PRR) of 23.36.[77] The olmesartan cases identified dated back to 2005. As FDA recognizes, a PRR is a data mining method that may give rise to a safety signal which requires further investigation.[78]

114. Herve Caspard, Daiichi Sankyo's Senior Director for Risk Management from 2009 to 2010 stated the following regarding PRR analysis at his deposition on April 7, 2016:

Q. Okay. So you talked about the Proportional Reporting Ratio.
A. Yes.
Q. That in fact is one of the epidemiological tools that you can use to analyze the information once you cast that net and bring it in, that you can use to analyze the data, correct?
A. Yes.
Q. Okay. And it's a generally accepted method of analyzing data in pharmacovigilance, correct?
A. Yes.
Q. In fact I think the guidance talks about it, correct?
A. Yes, it is -- it is imperfect, like, you know, any analysis of exceptional data, but it's the least -- one of the least bad indicators we have.
Q. Yeah. It's used fairly commonly amongst epidemiologists and biostatisticians in terms of

[76] Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. *Severe Spruelike Enteropathy Associated With Olmesartan*. Mayo Clin Proc. 2012 Aug;87(8):732-8. Epub 2012 Jun 22.

[77] *See* OLM-DSI-0005439763 – 76.

[78] *See* FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, p. 8 (2005).

21 signal analysis, correct?
22 A. I agree.
23 Q. Okay. And it's a valuable tool for you
24 to use in pharmacovigilance, correct?

88

1 A. It is. [79]

115. Regarding the PRR of 23.36 obtained by Daiichi Sankyo, Mr. Caspard testified:

11 Q. All right. 23.36 --
12 A. Is high.
13 Q. -- is a very high PRR, isn't it, doctor.
14 A. Yes. [80]

116. Mr. Caspard further testified regarding the PRR:

21 Q. Okay. That is -- and when we talk about
22 the 95% confidence interval and it being 23.36,
23 that means that your determination or the PRR shows
24 that there were 23 times more events than you would

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1 have expected on olmesartan as compared to all
2 other drugs, correct?
3 A. That's correct.
...
11 Q. Okay. And when we talk about the 95%
12 confidence interval, that means that, if you did
13 this test a hundred times, 95 of those times it
14 would be between the lower and upper bounds of the
15 confidence interval, correct?
16 A. Sorry. I have to be very careful about
17 this.
18 Q. Well, let me strike --
19 A. Yes.
20 Q. -- because I'm not trying to --
21 A. Yes, but I'm always struck by that.
22 Q. I know. The upper bound, let's just do
23 it this way, the upper bound, it could be, that
24 number, 23.36, could be as high as 36.77 –

108

[79] Deposition of Herve Caspard, April 7, 2016, at 87:1-88:1.

[80] *Id.* at 104:4-108:22.

A. Yes.
Q. -- or it could be as low as 14.05, correct?
A. Yes. Yes. The truth is somewhere in between.
Q. Okay. The truth is somewhere in between. And the best estimate you can give is 23.36 from a statistical standpoint.
A. Yes.
Q. Okay. But even at the lower bounds you're seeing 14 times more reports of celiac disease on olmesartan than you would have expected.
A. Yes.
Q. And that is a significant finding, correct, doctor?
THE WITNESS: From -- I have to characterize that -- statistically.
Q. It is a statistically significant finding, right, doctor?
A. Yes. [81]

117. Based on my search, the record does not show that the company did anything with this PRR result.

118. Fifth, in January 2010, in response to an FDA inquiry, Daiichi Sankyo stated that in 16 of 17 cases where olmesartan was restarted, there was a "recrudescence" of GI symptoms suggestive of celiac disease after restarting the drug. These rechallenge cases dated back to 2007. Daiichi Sankyo concludes in its response that an association between olmesartan and celiac disease is very unlikely, yet also concludes that olmesartan may exacerbate the symptoms of celiac disease.[82]

119. In my opinion, if Daiichi Sankyo concluded that olmesartan was associated with an exacerbation of celiac disease, Daiichi Sankyo had a duty to investigate to confirm whether this was the case. Based on my search, the record does not show the company acted on its

[81] *Id.* at 106:21-108:22.

[82] *See* OLM-DSI-0001247409 – 541.

conclusion that there were 16 cases of recrudescence of GI symptoms suggestive of celiac disease after olmesartan was restarted. In my opinion, a reasonable and prudent manufacturer, faced with these positive rechallenge cases, would conclude that warning about a causal link between olmesartan and celiac-like symptoms was appropriate.

120. In my opinion, any view that celiac disease was the culprit in the cases discussed in Section VI above was contradicted by the fact that 1) olmesartan did not contain gluten, as confirmed by Daiichi Sankyo[83]; and 2) celiac symptoms emerge in those patients with the condition when challenged and rechallenged by gluten, and there was no evidence of such a challenge and rechallenge pattern with gluten in the adverse event reports discussed above.

121. In my opinion, a reasonable and prudent drug manufacturer who attributes a "recrudescence" of celiac disease to their drug, when they conclude that their drug does not contain gluten, the known trigger of celiac disease, would investigate alternative causes.

122. Despite the fact that there was reproducible scientific evidence that met the FDA standard by 20006/2007 in Daiichi Sankyo's possession, Daiichi Sankyo failed to act on it and inform doctors and patients.

X. CONCLUSIONS

In my opinion[84]:

123. A drug manufacturer has a duty to revise the labeling of its drug "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."

124. A pharmaceutical manufacturer has an affirmative responsibility to look for and detect serious adverse reactions that can be associated with their drug.

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[83] *See* OLM-DSC-0001432320.

[84] For all my opinions, see the full Report.

125. A reasonable and prudent manufacturer should look for safety problems at all stages of drug development.

126. Positive de/rechallenge evidence that is reproducible meets the FDA standard of reasonable evidence of a causal association, and should trigger a Warning in the Warnings and Precautions section of the label.

127. There are multiple examples of FDA revising drug labels based on positive de/rechallenge evidence that support my opinion that positive de/rechallenge evidence that is reproducible meets the FDA standard of reasonable evidence of a causal association.

128. A reasonable and prudent manufacturer, faced with multiple positive rechallenge cases between olmesartan and gastrointestinal symptoms, would conclude that warning about a causal link between olmesartan and celiac-like symptoms was appropriate.

129. A reasonable and prudent manufacturer would have noted and acted upon the reproducible positive rechallenge data in Daiichi Sankyo's database.

130. Any view that celiac disease was the culprit in the adverse event reports discussed in Section VI above was contradicted by the fact that 1) olmesartan did not contain gluten, as confirmed by Daiichi Sankyo; and 2) celiac symptoms emerge in those patients with the condition when challenged and rechallenged by gluten, and there was no evidence of such a challenge and rechallenge pattern with gluten in the reports discussed above.

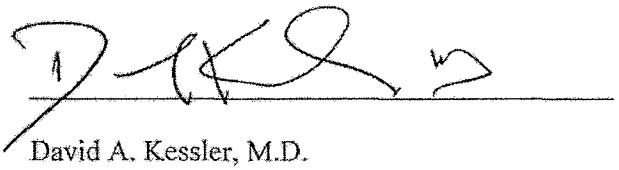
131. A reasonable and prudent drug manufacturer who attributes a "recrudescence" of celiac disease to their drug, would, when they conclude that their drug does not contain gluten, the known trigger of celiac disease, investigate alternative causes.

132. By the end of 2006, and no later than 2007, there was reproducible positive de/rechallenge evidence that met the FDA standard of reasonable evidence of a causal association.

133. Despite the fact that there was sound scientific evidence that met the FDA standard by the end of 2006, and no later than 2007, in Daiichi Sankyo's possession, Daiichi Sankyo failed to act on it and inform doctors and patients.

134. Daiichi Sankyo failed to adequately identify the safety problems associated with olmesartan associated enteropathy in a timely manner.

135. I reserve the right to supplement this Report based on new information.



David A. Kessler, M.D.

11/30/2016

Date

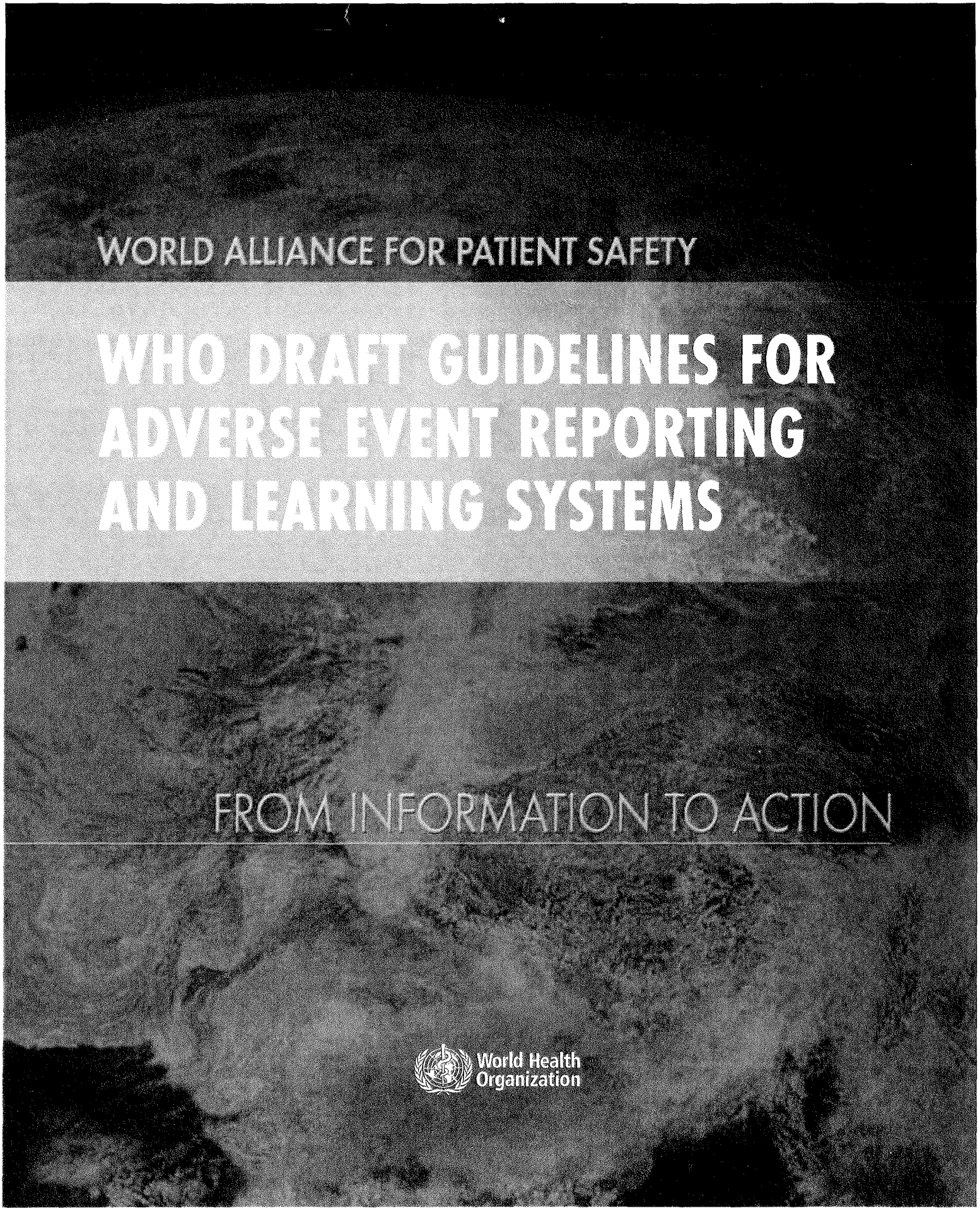
Exhibit W

Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			TOTAL SCORE:	

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

Exhibit X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FOREWORD

Imagine a jet aircraft which contains an orange coloured wire essential for its safe functioning. An airline engineer in one part of the world doing a pre-flight inspection spots that the wire is frayed in a way that suggests a critical fault rather than routine wear and tear. What would happen next? I think we know the answer. It is likely that – probably within days – most similar jet engines in the world would be inspected and the orange wire, if faulty, would be renewed.

When will health-care pass the orange-wire test?

The belief that one day it may be possible for the bad experience suffered by a patient in one part of the world to be a source of transmitted learning that benefits future patients in many countries is a powerful element of the vision behind the WHO World Alliance for Patient Safety.

The most important knowledge in the field of patient safety is how to prevent harm to patients during treatment and care. The fundamental role of patient safety reporting systems is to enhance patient safety by learning from failures of the health care system. We know that most problems are not just a series of random, unconnected one-off events. We know that health-care errors are provoked by weak systems and often have common root causes which can be generalized and corrected. Although each event is unique, there are likely to be similarities and patterns in sources of risk which may otherwise go unnoticed if incidents are not reported and analysed.

These draft guidelines are a contribution to the Forward Programme 2005 of the World Alliance for Patient Safety. The guidelines introduce patient safety reporting with a view to helping countries develop or improve reporting and learning systems in order to improve the safety of patient care. Ultimately, it is the action we take in response to reporting – not reporting itself – that leads to change.

Reporting is fundamental to detecting patient safety problems. However, on its own it can never give a complete picture of all sources of risk and patient harm. The guidelines also suggest other sources of patient safety information that can be used both by health services and nationally.

The currency of patient safety can only be measured in terms of harm prevented and lives saved. It is the vision of the World Alliance that effective patient safety reporting systems will help to make this a reality for future patients worldwide.

Sir Liam Donaldson

Chair
World Alliance for Patient Safety

TABLE OF CONTENTS

1. INTRODUCTION

Reducing medical errors has become an international concern. Population-based studies from a number of nations around the world have consistently demonstrated unacceptably high rates of medical injury and preventable deaths. In response, a global effort, the World Alliance for Patient Safety, has been launched by WHO to galvanize and facilitate efforts by all Member States to make health care safer.

These draft guidelines are a contribution to the Forward Programme 2005 of the World Alliance for Patient Safety (1). The guidelines introduce adverse event reporting and focus on reporting and learning to improve the safety of patient care.

Purposes of reporting

In seeking to improve safety, one of the most frustrating aspects for patients and professionals alike is the apparent failure of health-care systems to learn from their mistakes. Too often neither health-care providers nor health-care organizations advise others when a mishap occurs, nor do they share what they have learned when an investigation has been carried out. As a consequence, the same mistakes occur repeatedly in many settings and patients continue to be harmed by preventable errors.

One solution to this problem is reporting: by the doctor, nurse, or other provider within the hospital or health-care organization, and by the organization to a broader audience through a system-wide, regional, or national reporting system. Some believe that an effective reporting system is the cornerstone of safe practice and, within a hospital or other health-care organization, a measure of progress towards achieving a safety culture. At a minimum, reporting can help identify hazards and risks, and provide information as to where the system is breaking down. This can help target improvement efforts and systems changes to reduce the likelihood of injury to future patients.

Objectives

The objective of these draft guidelines is to facilitate the improvement or development of reporting systems that receive information that can be used to improve patient safety. The target audience is countries, which may select, adapt or otherwise modify the recommendations to enhance reporting in their specific environments and for their specific purposes. The guidelines are not meant to be an international regulation and will undergo modification over time as experience accumulates.

The guidelines draw on a review of the literature about reporting systems, a survey of countries about existing national reporting systems, and the experience of the authors.

Reporting may capture errors, injuries, non-harmful errors, equipment malfunctions, process failures or other hazards (see definitions below). While an individual report may contain important information about a specific incident or event, the notion of a reporting system refers to the processes and technology involved in the standardization, formatting, communication, feedback, analysis, learning, response, and dissemination of lessons learned from reported events.

Reports are generally initiated by health-care workers such as care providers or administrators from hospitals, ambulatory sites, or communities. Reporting systems may also be designed to receive reports from patients, families, or consumer advocates.

Definitions

Safety: Freedom from accidental injuries (2).

Error: The failure of a planned action to be completed as intended (i.e. error of execution) or the use of a wrong plan to achieve an aim (i.e. error of planning) (3). Errors may be errors of commission or omission, and usually reflect deficiencies in the systems of care.

Adverse event: An injury related to medical management, in contrast to complications of disease (4). Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse events may be preventable or non-preventable.

Preventable adverse event: An adverse event caused by an error or other type of systems or equipment failure (5).

"Near-miss" or "close call": Serious error or mishap that has the potential to cause an adverse event but fails to do so because of chance or because it is intercepted. Also called potential adverse event.

Adverse drug event: A medication-related adverse event.

Hazard: Any threat to safety, e.g. unsafe practices, conduct, equipment, labels, names.

System: A set of interdependent elements (people, processes, equipment) that interact to achieve a common aim.

nursing practice standards to label and trace all tubing, to a requirement for medical device manufacturers to develop incompatible connectors for all medical tubing.

Appendix 1 contains an excerpt from the landmark Institute of Medicine report To Err is Human, which provides an overview of the systems approach to human error within health-care and other industries.

Core concepts

The four core principles underlying the guidelines are:

- The fundamental role of patient safety reporting systems is to enhance patient safety by learning from failures of the health-care system.
- Reporting must be safe. Individuals who report incidents must not be punished or suffer other ill-effects from reporting.
- Reporting is only of value if it leads to a constructive response. At a minimum, this entails feedback of findings from data analysis. Ideally, it also includes recommendations for changes in processes and systems of health care.
- Meaningful analysis, learning, and dissemination of lessons learned requires expertise and other human and financial resources. The agency that receives reports must be capable of disseminating information, making recommendations for changes, and informing the development of solutions.

Organization of the Guidelines

Section 2 describes the role of reporting in enhancing patient safety, its purposes and the ways in which reporting can enhance safety.

Section 3 discusses the essential components of a patient safety reporting system, considering the types of systems, the process of reporting (what is reported, by whom, and how), analysis of reports, response and dissemination, and application of results.

Section 4 examines alternative sources of information for safety. Reporting is but one method of obtaining such information, not necessarily the best. Other sources of useful data are briefly described.

Section 5 provides information about several existing national reporting systems, both governmentally sponsored and those implemented by non-governmental agencies or groups. This illustrates the broad variation in how Member States have dealt with these issues.

Section 6 describes the characteristics of successful reporting systems. While experience is limited in health care, successful existing systems have common features in purpose, design and operation, that have general applicability.

Section 7 outlines the requirements for a national adverse event reporting system, including the mechanism for collecting reports, the capacity to perform investigations, the expertise required, the technical infrastructure, and the capacity to disseminate findings.

Section 8 concludes with recommendations to WHO Member States.

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2. THE ROLE OF REPORTING IN ENHANCING PATIENT SAFETY

Key messages

- **The primary purpose of patient safety reporting systems is to learn from experience.**
- **A reporting system must produce a visible, useful response to justify the resources expended and to stimulate reporting.**
- **The most important function of a reporting system is to use the results of data analysis and investigation to formulate and disseminate recommendations for systems change.**

The purpose of reporting adverse events and errors

The primary purpose of patient safety reporting systems is to learn from experience. It is important to note that reporting in itself does not improve safety. It is the response to reports that leads to change. Within a health-care institution, reporting of a serious event or serious "near-miss" should trigger an in-depth investigation to identify underlying systems failures and lead to efforts to redesign the systems to prevent recurrence.

In a state or national system, expert analyses of reports and dissemination of lessons learned are required if reports are to influence safety. Merely collecting data contributes little to patient safety advancement. Even monitoring for trends requires considerable expert analysis and oversight of the reported data.

The important point is that a reporting system must produce a visible, useful response by the receiver to justify the resources expended in reporting, or, for that matter, to stimulate individuals or institutions to report. The response system is more important than the reporting system.

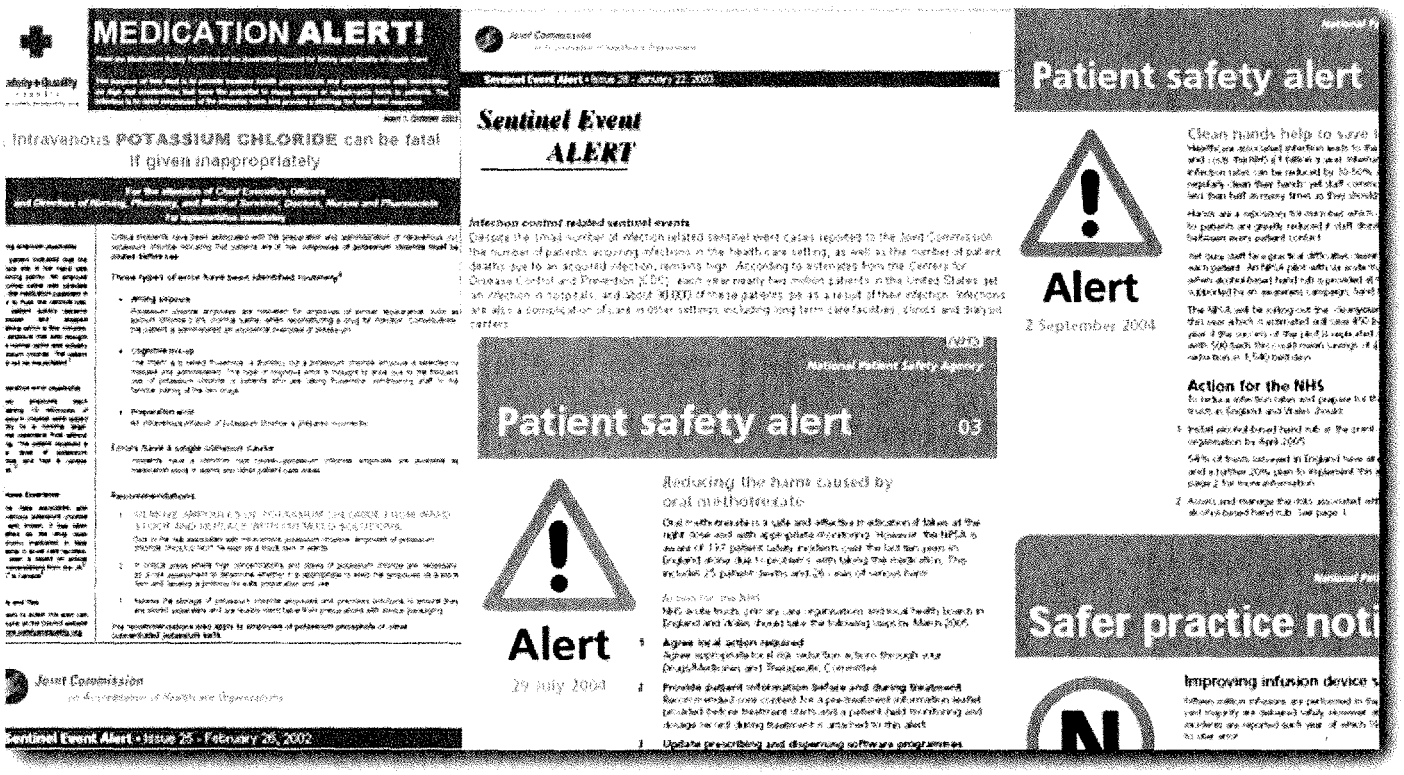
Methods of learning from reporting

There are several ways in which reporting can lead to learning and improved safety. First, it can generate alerts regarding significant new hazards, for example, complications of a new drug. Second, lessons learned by health-care organizations from

investigating a serious event can be disseminated. Third, analysis of many reports by the receiving agency or others can reveal unrecognized trends and hazards requiring attention. Finally, analysis of multiple reports can lead to insights into underlying systems failures and generate recommendations for "best practices" for all to follow.

Alerts

Even a small number of reports can provide sufficient data to enable expert analysts to recognize a significant new hazard and generate an alert. An excellent example of this function is the series of warnings issued every two weeks by the Institute for Safe Medication Practices entitled "Medication Alert". This system was one of the first to call attention to the high risk of death following accidental injection of concentrated potassium chloride and recommend that this substance be removed from patient care units.



Investigation of serious events

In a health-care organization committed to safety, a serious (especially disabling or life-threatening) event will trigger an investigation to search for underlying causes and contributing factors. Ideally, every institution will respond to a serious event with an investigation. Alternatively, an external authority (such as the health ministry) can conduct an independent investigation. If the investigation is done well, systems analysis of a serious adverse event can yield significant insights into the vari-

ous contributing factors that lead to a mishap, and often suggest potential remedies. This information can then be disseminated to other organizations. Solutions to some common hazards, such as wrong site surgery, have been developed in response to lessons learned from investigations of serious incidents.

Analysis of large datasets

Detailed analysis of thousands of reports also makes it possible to identify hazards (1). In the Australian Incident Monitoring System (AIMS) classification system, information about an incident is entered into the database using the generic classification scheme of clinically relevant categories. Natural questions guide analysts through details of context and contributing causes to probe interrelationships among event types, risk factors, and contributing causes. Statistical correlations identify meaningful relationships and provide analyses that can generate insights into the overall systems of care.

In the United States, USP's MedMARx[SM] system receives thousands of reports of medication errors and adverse drug events confidentially from participating health-care organizations. These data are classified and fed back to health-care organizations with benchmarking from the entire database and with their own prior experience, to identify targets for improvement as well as providing monitoring of progress.

Systems analysis and development of recommendations

The most important function that a large reporting system can perform is to use the results of investigations and data analyses to formulate and disseminate recommendations for systems changes. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has performed this function using a relatively small number of thoroughly investigated incidents reported to its sentinel events monitoring programme. Similarly, in the United States, some of the state reporting systems have developed safety recommendations from their data.

An example of a system aimed at translating learning into safety improvements is the relatively new National Reporting and Learning System (NRLS) developed by the National Patient Safety Agency (NPSA) in England and Wales. Reports are aggregated and analysed with expert clinical input to understand the frequency of types of incidents, patterns, trends, and underlying contributory factors. The NPSA has a "solutions" programme, involving all stakeholders. Recent initiatives include reducing errors associated with infusion devices, changes in doses of methotrexate, and a hand hygiene campaign.

Accountability

Some reporting systems, such as those of state health departments in the United States have been developed primarily to hold health-care organizations accountable for ensuring safe practice. Accountability systems are based on the notion that the government has a fiduciary responsibility to ensure that health-care organizations take necessary precautions to ensure that care is safe (2). A serious and presumably preventable injury, such as amputation of the wrong leg, suggests that the hospital's error prevention mechanisms are defective (3). Knowing that there is oversight by a government agency helps maintain the public's trust.

Accountability reporting systems hold health-care organizations responsible by requiring that serious mishaps be reported and by providing disincentives (citations, penalties, sanctions) to continue unsafe practices (4). Reporting in these systems can also lead to learning, if lessons are widely shared (2). However, if the government agency does not have sufficient resources to investigate or to analyse reports and disseminate results, the opportunity for learning is lost. In addition, the risk of sanctions may make health-care organizations reluctant to report events that can be concealed.

Since most reports elicit no response, and lessons from investigations are seldom shared, health-care organizations often perceive reporting in these systems as all risk and no gain (5). The result is that typical accountability systems receive relatively few reports. This is unlikely to change unless more resources are provided for analysis and reporting, and the consequences of reporting are made less punitive.

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3. COMPONENTS OF A REPORTING SYSTEM

Key messages

- **Current reporting systems span a spectrum of objectives incorporating both learning and accountability considerations.**
- **The primary objectives of a reporting system will determine the design, for example, whether reporting is voluntary and confidential.**
- **Reporting systems need to be clear on who reports, the scope of what is reported and how reports are made.**
- **Reporting of incidents is of little value unless the data collected are analysed and recommendations are disseminated.**
- **Experts who understand statistical methods, the practice concerns, clinical significance, systems issues, and potential preventive measures are essential to analyse reported incidents.**
- **Classification and simple analytic schemes start the process of categorizing the data and developing solutions that can be generalized.**

Types of systems

Current reporting systems span a spectrum of specific aims. At one end of the spectrum are reporting systems that focus on learning and contributing to system redesign. At the other end are systems developed by external regulatory or legal agencies primarily to ensure public accountability. These latter systems typically seek to identify health-care organizations where the level of care is unacceptable, for corrective action or discipline.

In practice, reporting systems may seek to address multiple objectives. Striking a balance within a single system between the aims of public accountability and learning for improvement is possible, but most reporting systems focus on one or the other. Although these aims are not necessarily incompatible, the primary objectives of the system will determine several design features, including whether the reports

are mandatory or voluntary, and whether they are held in complete confidence, or reported to the public or to regulatory agencies.

Learning systems

Reporting to learning systems is usually voluntary, and typically spans a wider scope of reportable events than the defined set of events typically required by a mandatory system. Rather than assure a minimum standard of care, learning systems are designed to foster continuous improvements in care delivery by identifying themes, reducing variation, facilitating the sharing of best practices, and stimulating system-wide improvements. Following careful expert analysis of underlying causes, recommendations are made for system redesign to improve performance and reduce errors and injuries.

In Australia, for example, over 200 health-care organizations or health services voluntarily send incident reports to the Australian Incident Monitoring System (AIMS) sponsored by the Australia Patient Safety Foundation (APSF). AIMS uses the Healthcare Incident Types (HIT) classification system, which elicits very detailed information from the reporter regarding generic incident types, contributing factors, outcomes, actions, and consequences.

The Japan Council for Quality Health Care collects voluntarily reported adverse events from health-care organizations in Japan, particularly sentinel cases with root cause analysis. A research team led by Tokai University asks health-care organizations to voluntarily pool their events, which are then aggregated and results disseminated. In 2003, the Ministry of Health, Labour and Welfare patient safety committee recommended a national reporting system.

The National Reporting and Learning System (NRLS) in England and Wales is another example of a learning system. NRLS receives reports of patient safety incidents from local health-care organizations.

For more details about the above systems, see Section 5.

Accountability systems

Reporting in accountability systems is usually mandatory and restricted to a list of defined serious events (also called "sentinel" events) such as unexpected death, transfusion reaction, and surgery on the wrong body part. Accountability systems typically prompt improvements by requiring an investigation and systems analysis ("root cause analysis") of the event. Few regulatory agencies have the resources to perform external investigations of more than a small fraction of reported events, however, which limits their capacity to learn. In Slovenia, a brief description of a sentinel event must be sent to the Ministry of Health within 48 hours, and 45 days later a satisfactory analysis with corrective actions must be submitted or else a follow-up consultation with the Ministry occurs. The Czech Republic has reporting requirements that follow from their accreditation standards.

The Netherlands has a two-tiered process. The Health Care Inspectorate, the agency accountable for taking actions against substandard performance, mandates hospitals to report adverse events that have led to death or permanent impairment. Other adverse events are reported voluntarily. There is interest in moving towards a more uniform blame-free reporting system to aggregate events nationally.

A number of states in the United States have reporting systems that require hospitals or other providers to report certain types of serious, usually preventable events (see Section 6).

Most accountability systems not only hold health-care organizations accountable by requiring that serious mishaps be reported, they provide disincentives to unsafe care through citations, penalties or sanctions. The effectiveness of these systems depends on the ability of the agency to induce health-care organizations to report serious events and to conduct thorough investigations.

Accountability systems can (and should) be learning systems if investigations are carried out and if the lessons learned are disseminated to all other providers by the agency. For example, the Danish Health Care System recently passed an Act on Patient Safety that requires health-care providers to report adverse events so information can be shared and aggregated for quality improvement.

Confidentiality and public access to data

Experience has shown that learning systems are most successful when reports are confidential and reporters do not feel at risk in sharing information about errors. Indeed, some feel it is only with such safe reporting systems that subtle system issues and the multitude of contributing factors will be uncovered. From a pragmatic standpoint, many believe that protecting the confidentiality of health-care organizations significantly enhances participation in reporting (1, 2).

However, some citizen advocacy groups have called for public disclosure of information uncovered during investigations of serious adverse events, asserting the public's right to know about these events. Surveys in the United States show that 62–73% of Americans believe that health-care providers should be required to make this information publicly available (3, 4). Nonetheless, all but three states in the United States have statutes that provide legal protection of confidentiality (5).

Internal reporting

Reports to an agency or other national body from a hospital or other health-care organization usually originate from a report within the institution. While such reports may merely reflect statutory requirements, an institution that values patient safety will have an internal reporting system that captures much more than that.

The objectives of an internal reporting system for learning are first, to identify errors and hazards, and then through investigation to uncover the underlying sys-

tems failures, with the goal of redesigning systems to reduce the likelihood of patient injury. The key conceptual point here, and the heart of a non-punitive approach to error reporting, is the recognition that adverse events and errors are symptoms of defective systems, not defects themselves. Reporting, whether retrospective (adverse events and errors) or prospective ("hazards", or "errors waiting to happen") provides the entry point into investigation and analysis of systems' defects, which, if skillfully done, can lead to substantial system improvements. Reporting is one way to get this type of information, but not the only way (see Section 4).

Ideally, internal reporting systems should go hand in hand with external reporting systems, by identifying and analysing events that warrant forwarding to external reporting agencies. Conversely, external reporting systems are most effective when they are an extension of internal systems.

Process

What is reported

Types of reports

Reporting systems may be open-ended and attempt to capture adverse events and close-calls along the entire spectrum of care delivery, or may focus on particular types of events, such as medication errors or pre-defined serious injuries. In general, focused reporting systems are more valuable for deepening the understanding of a particular domain of care than for discovering new areas of vulnerability. While these guidelines focus on reporting systems related to adverse events and medical errors, other types of health-related reporting systems focus on medical devices, epidemiological outcomes such as emergence of antimicrobial resistance, post-marketing medication surveillance, and specific areas such as blood transfusions.

Formats and processes vary from prescribed forms and defined data elements to free-text reporting. The system may allow for reports to be submitted via mail, telephone, electronically, or on the World Wide Web.

Types of events

Adverse events. An adverse events is an injury related to medical management, in contrast to a complication of disease (6). Other terms that are sometimes used are "mishaps", "unanticipated events" or "incidents", and "accidents". Most authorities caution against use of the term accident since it implies that the event was unpreventable.

Adverse events are not always caused by an error. For example, one form of adverse drug event, "adverse drug reaction" is, according to the WHO definition, a complication that occurs when the medication is used as directed and in the usual

dosage (7). Adverse drug reactions are, therefore, adverse drug events that are not caused by errors.

Many adverse events are caused by errors, either of commission or omission, and do, in fact, reflect deficiencies in the systems of care (8). Some reporting systems require that only preventable adverse events be reported, while others solicit reports whether or not a medical error occurred. One advantage of focusing reporting on adverse events rather than on errors is that it is usually obvious when a mishap has occurred; actual events focus attention.

Error. Error has been defined as "the failure of a planned action to be completed as intended (i.e. error of execution) or the use of a wrong plan to achieve an aim (i.e. error of planning)" (9). Although reporting of errors, whether or not there is an injury, is sometimes done within institutions, if reporting of all errors is requested, the number may be overwhelming. Therefore, some sort of threshold is usually established – such as "serious" errors, or those with the potential for causing harm (also called "near misses" or "close calls"). Establishing such a threshold for a reporting system can be difficult. Hence, most "error reporting systems" are actually "adverse events caused by errors" systems.

"Near miss" or "close call". " A near miss" or "close call" is a serious error or mishap that has the potential to cause an adverse event, but fails to do so by chance or because it was intercepted. It is assumed (though not proven) that the underlying systems failures for near misses are the same as for actual adverse events. Therefore, understanding their causes should lead to systems design changes that will improve safety.

A key advantage of a near miss reporting system is that because there has been no harm the reporter is not at risk of blame or litigation. On the contrary, he or she may be deserving of praise for having intercepted an error and prevented an injury. This positive aspect of reporting of near misses, has led some to recommend near miss systems for internal reporting systems within health-care organizations or other health-care facilities where a blaming culture persists. However, any hospital that is serious about learning will also invite reports of near misses.

Hazards and unsafe conditions. Reporting of hazards, or "accidents waiting to happen" is another way to achieve prevention without the need to learn from an injury. If health care were as safe as some other industries, reports of hazards – potential causes of adverse events (as opposed to near misses, which are actual errors) – would outnumber those of actual events. Of all major systems, the Institute for Safe Medication Practices system for medication-related events has been most successful at capturing hazards (e.g. "look alike" packaging and "sound alike" names.) and calling for their remedy before a predictable error occurs.

Within a health-care organization, hazard reports raise alerts about unsafe conditions. Providers can imagine accidents waiting to happen based on their observations of weakness in the system and their experience as users. With appropriate analysis, these reports can provide valuable information for changes to systems design.

Who reports

Reporting systems must specify who files reports. In accountability systems, such as state health department systems and the JCAHO in the United States, reporting is done by the organization. Many also solicit and receive reports from caregivers (doctors and nurses). Some jurisdictions require caregivers to file reports. Some reporting systems allow patients, families and consumer advocates to report events. The latter are typically merely a notice that an event has occurred. In general, learning systems solicit reports from caregivers or organizations. Focused systems targeting specific areas such as medication errors or intensive care errors solicit reports from specialists such as pharmacists or intensive care specialists, while broad-based systems look to organizations and caregivers, but usually accept reports from anyone.

A potential source of reports that has not been significantly used is patients and families who have experienced medical error. Patients often report a high desire to see remedial action taken to prevent future harm to others. Reporting can initiate that process. Patients may report otherwise unidentified issues that help health-care organizations understand where the holes in their safety nets are, identify root causes, and mitigate harm. A patient may experience an injury that does not manifest until after discharge from a hospital and therefore is not otherwise captured. Patients may be better positioned than their care providers to identify failures in hand-overs and gaps between providers across the continuum of care.

How do they report

Method: e-mail, fax, Internet, mail, phone calls

Methods for submitting reports vary according to local infrastructure and technology. They can range from mailing written reports to a central address, to web-based systems that centralize and aggregate multiple reports into a highly structured database. Mail, fax, and phone calls are most widely used, since these mechanisms are widely available. A streamlined process can be set up to receive reports by e-mail or over the Internet; for users who have access to these technologies, this can be very quick and easy (although it may be costly to establish the technical infrastructure). Systems that use e-mail or the Internet must be able to provide technical support for users.

Structured forms or narrative text

Reports may be highly structured, requiring specific types of information, or provide for a narrative description of events for analysis. The extent to which datasets can be developed for analysis depends in part on the degree of standardization inherent in the data reported. Events based on commonly accepted data elements, such as the classification of medication errors into wrong medication, wrong dose, wrong frequency and so on, can be readily configured into a standardized reporting format.

A higher level of structured reporting asks reporters to select options from defined fields as part of the reporting process. This can greatly facilitate input into datasets developed for analysis. The Australian Patient Safety Foundation's Advanced Incident Management System (AIMS), offers a highly sophisticated customizable data entry form that guides users through a cascade of natural questions and response choices that are structured and consistent.

However, much of what promotes learning in patient safety lacks crisply defined data elements, so most authorities believe it is important for reports to include narrative to convey meaning. Narrative reports provide the opportunity to capture the rich context and storyline that allow the conditions that contributed to the error to be explored and understood. Indeed, some believe that only narrative reports are capable of providing information that provides meaningful insight into the nature of the underlying systems defects that caused the incident (Richard Cook, personal communication).

The vast majority of reporting forms have at least some room for a narrative description, and some, such as the United States Food and Drug Administration (FDA) MedWatch programme include open narrative for other relevant medical information such as laboratory data or patient condition.

Because of the nature of analysis that is required, systems that elicit open-ended, narrative texts require additional resources for data analysis and interpretation. In contrast, reports to systems with a standardized format, fixed fields, and predefined choices are swiftly entered and readily classified, making possible aggregated analysis at lower cost.

Another consideration is the effect of reporting on the reporter. Providing reporters with the chance to tell their stories implicitly values their observations. When the reporter can trust in a considered and non-punitive response, the process raises the individual's awareness of patient safety and sense of responsibility for reporting.

Classification

Reporting of events is of little value unless the data are analysed. Regardless of the objective of the system – whether to identify new and previously unsuspected hazards, discover trends, prioritize areas for remedial efforts, uncover common contributing factors, or develop strategies to decrease adverse events and patient harm – neither the act of reporting nor the collection of data will accomplish that objective unless the data are analysed and recommendations are made for change. Classification of the event is the first step in the analysis.

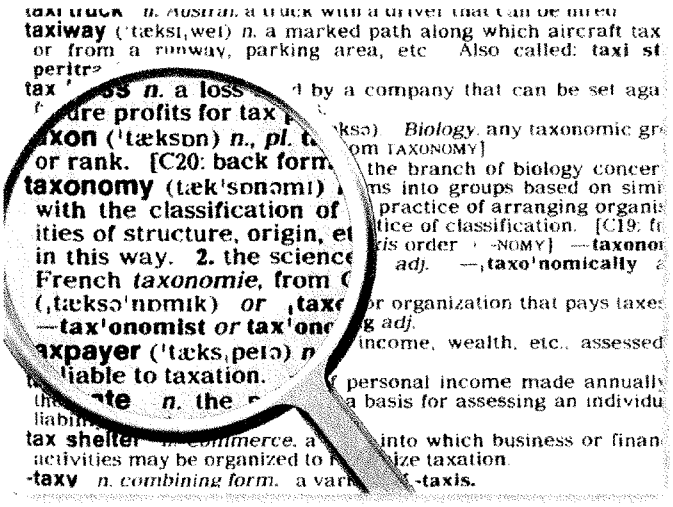
Why classify?

Recall the case presented in Section 1 of the inadvertent connection of oxygen tubing to an intravenous line the result being an air embolism. After the incident is reported, classification by the reporting system turns a specific event into an example that could happen anywhere; this particular incident becomes an example of "tubing mix-up". When aggregated with similar incidents, depending on the availability of contextual information, a variety of solutions can emerge, ranging from changes in nursing practice standards to a requirement for medical device manufacturers to develop incompatible connectors for all medical tubing. Classification starts the process of developing solutions that can be generalized.

Classification systems (taxonomies)

A number of quite different systems have been used for classifying patient safety incidents. These systems are also called "taxonomies". Because of differences between taxonomies, data can often not be shared among systems. Further, none have been validated, in the sense of studies that demonstrate that the classification and analysis method used leads to significant improvements in patient safety. As a result, the WHO World Alliance for Patient Safety has included in its Forward Programme 2005 an action area focusing on the development of an internationally agreed taxonomy of events.

Some of the factors that have been used to classify events include: error type (wrong dose, wrong diagnosis, etc.), patient outcome (level of harm, from none to death), setting, personnel involved, product or equipment failures, proximal (obvious) causes (misidentification of a patient), underlying causes (lack of knowledge, information, skills, etc.), contributing factors (organizational factors, environmental factors, etc.), stage in process of care (ordering, implementation, responding to laboratory results), and mechanism of error (knowledge-based, rule-based, skill-based). These taxonomies tend to fall into three major categories: classification by event, by risk, or by causation.


taxiway ('tæksɪˌweɪ) *n.* a marked path along which aircraft tax
or from a runway, parking area, etc Also called: **taxi st**
tax *n.* a loss
ure profits for tax
axon ('tæksɒn) *n., pl.* **t**
or rank. [C20: back form
taxonomy (tæk'sɒnəmɪ)
with the classification of
ities of structure, origin, et
in this way. **2.** the science
French *taxonomie*, from
(ˌtæksə'nɒmɪk) *or* **taxe**
—tax'onomist *or* **tax'one**
axpayer ('tæksˌpeɪə) *n*
liable to taxation.
te *n.* the
tax shelter
activities may be organized to
-taxy *n. combining form.* a var
by a company that can be set aga
Biology. any taxonomic gr
the branch of biology concer
practice of arranging organis
adj. **—taxo'nomically**
organization that pays taxes
income, wealth, etc., assessed
personal income made annually
basis for assessing an individu
into which business or finan
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A taxonomy of adverse events classifies by event type, such as how many medication errors are attributable to "wrong dose" or "wrong patient". Event classification schemes work best when describing a specialized medical domain, such as medication errors, dialysis events or transfusion mismatches.

Several systems use taxonomies to assess risk, in order to prioritize events for action or to determine if further investigation is warranted. The United States Pharmacopoeia (USP) uses a nine-tier approach to rank medication risk. The Veterans Health Administration (VHA) uses a scoring system to prioritize both the potential severity, and the likelihood of occurrence of events, based on specific

scales and definitions; these are organized into a "safety assessment code" matrix (10). See Figure below.

The Australian Patient Safety Foundation uses explicit criteria for assessing the degree of risk expressed as a risk matrix that plots the severity of the outcome against the likelihood of its recurrence (11). The United States Agency for Healthcare Research and Quality (AHRQ) has indicated that a risk assessment scale should be included in its Patient Safety Network reporting system currently being developed in collaboration with the Institute of Medicine's Committee on Data Standards for Patient Safety

Figure: Safety Assessment Code (SAC) Matrix

		SEVERITY			
		Catastrophic	Major	Moderate	Minor
PROBABILITY	Frequent	16	12	8	4
	Occasional	12	9	6	3
	Uncommon	8	6	4	2
	Remote	4	3	2	1

Source: Veterans Health Administration National Center for Patient Safety, United States of America

The earliest classification system that focused on causation was the Eindhoven Classification Model, developed at Eindhoven University of Technology in the Netherlands. It is used in high-risk industries such as chemical manufacturing. It has recently been adapted for use in the VHA root cause analysis to identify factors based on the principles of human, organizational, and technical factors.

Another causation-oriented system is the Australian Incident Monitoring System developed by the Australian Patient Safety Foundation. This classification system comprises more than a million permutations of terms to describe an incident or adverse event. The system allows the end user to deconstruct an incident into a very detailed data set that defines the relationships between the component factors of the classification system.

A related system is classification by contributing factors, used at the Clinical Risk Unit at University College in London, England to identify patient, provider, team, task, work environment, organizational and other factors, through comprehensive systems analysis (12).

Design of a classification system

At least three key factors should be considered in the design of a classification system:

- The purpose of the reporting system. What is the expected product? How will the classification scheme facilitate analysis that will produce the desired outcome?
- The types of data that are available. Are reporters expected to have carried out an investigation and analysis of the event? If not, it is

unlikely that they will be able to provide useful information concerning underlying systems causes, and events will not be able to be classified at that level.

- Resources. The more detailed and elaborate the classification system is, the more expertise will be required, and the costlier the system will be to maintain.

A report commissioned by WHO and prepared by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) notes that the following attributes are desirable in an ideal classification scheme (13):

- It should address a broad and diverse range of patient safety issues and concerns across multiple health-care settings.
- It should identify high-priority patient safety data elements that are important to health-care systems.
- It should classify information related to what, where and how medical management goes wrong, the reasons why medical incidents occur, and what preventive and corrective strategies can be developed to keep them from occurring or to ameliorate their effects in health care.
- It must provide a meaningful and comprehensive linkage between the contributory factors and the errors and systems failures that lead to adverse events.
- It should facilitate the monitoring, reporting, and investigation of adverse events and near misses at the public health level – allowing aggregated data to be combined and tracked.

Because the resources required for taxonomy and analytical development tools are substantial, development of classification schemes is probably better left to national or international agencies rather than individual health-care systems.

The role of classification

Classification can be the cornerstone of what the system does. If the main goal is to produce data on the frequency of different types of events, as in the USP MedMARx[SM] system, then performing the classification, determining frequencies, and feeding back that information may be all that is needed to meet the objective of the reporting system.

More commonly, classification is the beginning of more complex analysis, the first step. A direct link exists between the type and complexity of the classification scheme, and the level of analysis that is possible. That is, the analytic plan should determine the classification scheme, not the reverse.

Analysis

Hazard identification

At a minimum, a reporting system should permit identification of new and unsuspected hazards, such as previously unrecognized complications associated with use of a medication or a new device. A simple way this can be done is by direct human review of incoming reports. For example, if even a few people report that free flow protection on a particular pump model can fail, that may be sufficient for the receivers of the reports to recognize the problem, alert the providers and communicate directly with the pump manufacturer.

This type of analysis requires that knowledgeable experts review reports, but the reports do not need to be based on extensive investigation by the reporting organization. A good example of a hazard identification model is the Institute for Safe Medication Practice (ISMP) Medical Error Reporting Program, where a small group of pharmacists reviews all reports, identifies new hazards, and prioritizes them for action. Recommendations are then disseminated to the participants (most hospitals) every two weeks via a newsletter, Medication Safety Alert.

Both JCAHO, through its sentinel events alert warning and ISMP have legitimately taken credit for the success in removing concentrated potassium chloride from nursing units in the United States (14). ISMP alerts have also led to drug name and label changes, as well as the removal or restriction of the use of many drugs (15). MedMARx[SM] analysis revealed reports of three drugs with a high frequency of medication errors: insulin, heparin, and warfarin (16).

Summaries and descriptions

At the next level, a simple classification scheme can provide summaries and descriptions that permit determination of frequencies or ranking by order of frequency. An example of this would be a reporting system that records medication errors classified by dose, route, patient, etc. Calculating frequencies permits prioritization that can be used by focused systems to allocate further resources.

Trend and cluster analysis

Trend analysis, obtained by calculating and observing rates of events over time, can identify significant changes that suggest new problems (or, if improving, that safety measures are working). Trends can also be detected using statistical control methodologies. These assist a particular organization in discerning whether its own trends, when compared with benchmarks, are attributable to what is known as "special cause" variation, rather than stemming from normal process fluctuations.

A cluster of events that suddenly arises suggests a need for inquiry. It is important to note that trends or clusters identified by reporting systems are those of reported events, not those of the events themselves. For example, the JCAHO recently released a sentinel event alert concerning wrong site surgery when the rate of reports it received increased substantially over a two-year period. However, it acknowledged that only a small fraction of events are reported, so the data may not be representative. The United States Pharmacopeia (USP) MedMARxSM system analyses events to identify trends. Such trends may influence standard-setting practices. Large-scale reporting systems such as the National Reporting and Learning System, of the National Health Service in England, also provide pattern analysis and recognition of trends or clusters (17).

Correlations

While trends over time or control charts are ways of using the factor of time, other analytical methods are available for additional cofactors. To take the example of 'medication error – wrong patient', other factors captured may include, for example, the health-care setting (whether clinic or hospital), the patient diagnosis, or the age of the patient. These can be subjected to an analysis of correlations to evaluate the strength of the relationship between two variables, such as whether dosing errors occur more frequently among chemotherapy patients than among patients undergoing other treatments, or whether wrong patient medication errors are more highly correlated with elderly patients than with younger (and perhaps more alert) patients.

Risk analysis

With adequate data, a reporting system can develop valuable information about risk. With a large number of reports, estimations of the probability of recurrence of a specific type of adverse event or error can be calculated. Analysis of reported outcomes can also produce an estimate of the average severity of harm caused by the incident. The Safety Assessment Code of the United States Veterans Health Administration uses these two factors, probability of recurrence and severity, to calculate a score for prioritizing incidents for safety initiatives.

Causal analysis

When many factors are classified and coded along with the event, a more complex set of correlations and relationships among the factors can be considered and tested in the database. If causal factors such as workloads, communication, teamwork, equipment, environment, staffing and the like are included, then correlations among many cause and effect relationships can yield important insights into a health-care system's vulnerabilities.

Another analytical tool that can be applied to datasets with a rich set of cofactors is regression analysis, which assesses the predictive value of multiple factors upon

the outcome. For example, regression analysis can be used to investigate whether patient diagnosis is a predictive factor for dosing error. The major use for this analytical approach is to go beyond identifying relationships to hypothesis testing.

The sentinel event alerts issued by JCAHO include risk reduction strategies based on causal analyses submitted with reports, such as finding that medication errors attributable to illegible handwriting or poor communication are more common when abbreviations are used. Eliminating abbreviations has thus become one of the JCAHO patient safety goals for hospital accreditation.

Systems analysis

The ultimate aim of reporting is to lead to systems improvements by understanding the systems failures that caused the error or injury. At the organizational level, this requires investigation and interviews with involved parties to elicit the contributing factors and underlying design failures. A national reporting system must receive this level of information in order to identify common and recurring systems failures. For example, if analysts repeatedly find similar underlying systems defects in reports of a specific type of error, then remedial actions should focus on correction of that failure.

The Australian Patient Safety Foundation identified problems with valve-controlled flow and pressure occurring with anaesthetic machines. Query of the database provided a deconstruction of the malfunction types and suggested, among other things, that frequent maintenance and audible alarms on pressure relief valves could prevent these mishaps (18).

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4. ALTERNATIVE SOURCES OF INFORMATION FOR PATIENT SAFETY

Key messages

- **Reporting systems are clearly of value for learning from others' experience.**
- **Reporting systems do not provide a complete picture of risks, hazards and system vulnerabilities.**
- **There are other valuable sources of information that can be used within a health service and nationally to complement reporting.**
- **These options may present less expensive options than establishing national reporting systems.**

National or system-wide reporting systems are clearly of great value for learning from others' experience. Many adverse events occur rarely, and thus to observers in the institution may seem to be isolated (outlier) cases. Commonality and common causation only emerge with analysis of aggregated data. Similarly, demonstrating occurrence of serious events in respectable peer institutions helps counteract a typical response of "that could never happen here", which providers may genuinely feel when asked about a serious adverse event, such as amputation of the wrong leg.

However, there are other valuable sources of patient safety information that can be used at both the internal health-care organizational level and nationally. Many are much less expensive, and therefore constitute important options for states and health-care organizations that are unable to finance a large reporting system. They are worthy of consideration even for those with highly developed reporting systems. We look at internal options first.

Internal alternative sources of safety information

An effective internal reporting system is an essential component of a hospital patient safety programme. However, even a simple reporting system can be a significant expense. For many institutions, providing the financial resources and expertise required to establish a reporting system may be a burden, and may not be the wisest use of scarce funds. Another problem is compliance. Studies have repeatedly shown that many events are not captured by typical reporting systems. Personnel often fail

to make reports for a host of reasons: because they forget, are too busy, or think it is unimportant, or because the reporting does not lead to significant change. Too often, failure to report reflects a punitive environment in which it can be harmful to the reporter or colleagues to report.

Fortunately, reporting is not the only way to obtain information about hazards and systems defects. Hospital personnel – nurses, pharmacists, doctors, risk managers, and others – are a rich source of information that even well run reporting systems do not fully exploit. Medical records, laboratory reports, and other routinely collected data can also be used to find evidence of safety problems. Several methods that have been found useful for utilizing these resources are described in this section. In addition, several alternative methods for collecting data on quality and safety of care are described that do require more extensive resources but offer the promise of more complete and less intrusive data collection. These alternatives are presented in order of increasing resource intensity.

Safety WalkRounds

A "Safety WalkRound" is a process whereby a group of senior leaders visit areas of a health-care organization and ask front-line staff about specific events, contributing factors, near misses, potential problems, and possible solutions. The leaders then prioritize the events and the patient safety team develops solutions with the clinicians. The results are fed back to the staff (1).

The information gleaned in this process often has the solution embedded in the event description. Thus, this process can often result in prompt changes that improve care and safety. It also can lead to culture change, as the concerns of front-line staff are addressed and as front-line staff are engaged in continuous observation of hazards and solutions for discussion with senior leadership. Leadership walkrounds are a low-cost way to identify hazards of concern to front-line staff and make needed changes. They require no additional staff, equipment, or infrastructure.

Focus groups

Focus groups are facilitated discussions with staff or with patients and families to elicit insights, concerns, and perceptions in an open, learning environment. Most nurses, for example, are aware of hazards in their daily work, accidents "waiting to happen", and are willing to discuss them if given the opportunity. A few hours with front-line people can generate a safety improvement agenda that will keep a hospital busy for months.

Focus groups offer an opportunity for a very rich learning environment as members within the group discuss and develop ideas. While this method of information gathering cannot provide trends or benchmarks like a reporting system, it can identify both hazards and potential solutions that otherwise remain hidden.

Medical record review

Medical record review has historically been the major method for oversight of quality. While labour intensive, record review often provides the reviewer with the story and context in which to understand events. In addition, medical record review allows for evaluation of processes as well as outcomes, and can yield information about whether important processes occurred, such as communication, documentation, use of a checklist, or administration of an evidence-based therapy.

Record reviews may be explicit, in which the reviewer searches for specific types of data that define events (such as "failure to rescue") or implicit, in which a clinical expert makes a judgment as to whether an adverse event and/or error has occurred (such as failure to follow up a positive laboratory test). Record reviews have been the cornerstone of the major population-based studies that defined the extent of medical injury (2-6). They are also widely used to monitor progress in preventing adverse events when new safe practices are implemented.

The major limitations of record review are its cost, and variability of content. Aside from laboratory reports and orders, much of the content is determined by the subjective judgments of those who write notes. While serious adverse events are almost always mentioned, errors and underlying conditions almost never are. "Near misses" are rarely noted. Thus, records can be valuable for case finding, but provide only limited contextual information.

Focused review

Medical record reviews that focus on a specific type of event can identify critical points of care that represent widespread vulnerabilities. Focused reviews of adverse drug events, for example, might show that ordering medications for patients with renal impairment, managing anticoagulation, and tracking allergies are areas that warrant widespread, systematic improvements. A focused record review might reveal not only the incidence of wrong-site surgery, but also whether a site checklist was executed and a time-out took place during each operation. Other focused analyses might include identifying high complexity processes.

Failure modes and effects analysis

Adverse events can be viewed as the outcomes of vulnerable systems. In addition to acquiring information about the outcomes, or events, it is very helpful to learn about the vulnerabilities in the system and about possible solutions to buffer and strengthen the systems of care.

Failure modes and effects analysis (FMEA) is a widely used tool for proactively identifying process vulnerabilities. It begins by systematically identifying each step in the process and then searches out "failure modes", that is, noticing what could go wrong. The next step is to evaluate how the failure mode could occur, and what are the "effects" of this failure. If a failure mode could result in catastrophic effects, the

process must be corrected or buffered. The FMEA is a proactive tool, used to evaluate a new process, or an existing process for proposed design changes.

Screening

Screening is the use of routine data to identify a possible adverse event. It can be performed retrospectively, or in "real" time, either by analysis of traditional paper records or automatically by computer programs if patient clinical and laboratory data are available in electronic form. "Occurrence" screening identifies when a predefined event occurs, such as a return to the operating room within an admission or a readmission for the same problem.

Screening criteria are sometimes referred to as "triggers". When a screening criterion is met, further investigation, usually in person by an expert, is needed to determine whether an event has, in fact, occurred.

For example, laboratory data can be screened for out of range International Normalized Ratio (INR) results in patients taking warfarin. Records of patients with a positive screen – defined as values above or below a defined range – are then reviewed to determine if an episode of haemorrhage or thrombosis has occurred.

The Institute for Healthcare Improvement (IHI) has pioneered in the use of a "trigger tool" to retrospectively discover adverse drug events (ADE) (7). Records are searched for the presence of any of a list of highly sensitive indicators (such as prescribing a narcotic antidote or out of range INR). If the trigger is found, further investigations are carried out to determine if the ADE did in fact occur. This tool can be used both to assess the rate of selected ADEs and to measure progress when new safe practices are implemented.

Observation

The observation method for discovering errors consists first of a knowledgeable expert (such as a nurse or pharmacist) observing a process and writing down precisely the steps that are taken by the provider. This log is then compared with the written orders to identify deviations. Observational studies of nurse administration of medications in a large number of hospitals have shown high error rates (average 11% of doses) (8). The nurses were not aware of the errors which would, thus, not be captured in a reporting system.

The observation method is very labour-intensive, and therefore costly. However, it yields very rich data that facilitate understanding, not only about what events occur, but also about the processes and dynamics that affect the outcome. It is a tool that can be used intermittently, as resources permit, both to identify and understand systems breakdowns and to monitor improvement after changes are implemented.

Observing the hand-over during a transition between caregivers, for example, will yield not only whether there is an error, but also meaningful clues as to the barriers

and solutions. Observation can also identify areas where process designs such as standardization, simplification, and forcing functions may be useful to avoid harm.

External alternative sources of safety information

At the national or systems level, alternatives to reporting have not been widely employed. Medical record reviews have been occasionally used in random audits to identify adverse events and estimate frequency. Specific one-off studies, such as the Confidential Enquiries in the United Kingdom have served this function for several decades (9,10). This type of sampling can identify system weaknesses that require attention with much fewer resources than required by a reporting system. Several other methods of gathering safety data are available, as described below.

Malpractice claims analysis

Where frequent, as in the United States, malpractice claims can provide a rich source of data concerning a small number of serious events. When a serious incident occurs, risk managers typically start a patient file (called a claim, even if no litigation ever ensues) and promptly conduct an investigation, interviewing all personnel involved to understand and correctly document exactly what happened. This type of analysis, while much less sophisticated than a root cause or systems analysis carried out by experts, produces far more information than the usual hospital reporting systems.

Analysis of claims, for example, has identified the factors that increase the probability of a foreign body being retained following surgery and demonstrated the need for fail-safe follow-up systems to ensure that positive mammograms lead to biopsy (11).

The limitation of malpractice claims is their non-representativeness. However, they do provide data on events that are significant – serious injuries – as well as data that are typically much more comprehensive than provided to most reporting systems.

Surveillance

Surveillance systems collect specific case data, checking for predefined factors and outcomes on all patients in a defined category (such as those with infection). These systems can identify the prevalence of risk and risk factors for key events, as well as provide benchmarks for organizations and assist in monitoring progress.

One of the best examples of a surveillance system is the National Nosocomial Infections Surveillance System, a voluntary, confidential cooperative effort between the United States Centers for Disease Control and Prevention (CDC) and participating hospitals to identify hospital-acquired infections and create a national database that is used to understand the epidemiology of nosocomial infections and antibiotic

resistance trends, and to provide robust benchmarks for organizations to track their own performance (12,13).

Another form of surveillance focuses on review of hospital discharge diagnostic codes. A list has been developed in the United States by the Agency for Healthcare Research and Quality (AHRQ) of specific discharge codes, called Patient Safety Indicators (PSI), that are highly correlated with "problems that patients experience as a result of exposure to the healthcare system and that are likely amenable to prevention"(14). Examples include retention of foreign bodies, complications of anaesthesia, obstetric trauma, decubitus ulcers, and postoperative hip fracture. Hospitals can use the PSI to identify potential systems failures and to monitor improvement in safety. As the indicators are refined, it seems likely that they will be used in a national monitoring programme.

Routine data collection

A variant of surveillance on a much larger scale is exemplified by the United States Veterans Health Administration National Surgical Quality Improvement Program (NSQIP) (15). Trained surgical clinical nurse reviewers collect data on 129 clinical and outcome variables (including 30-day postoperative outcomes) for all major operations performed at each Veterans Health hospital. These data are electronically transmitted to a coordinating centre that uses predictive models to generate risk-adjusted predicted probability of death or complications for each patient.

Observed and expected ratios of complication rates and mortality are then calculated for each hospital and service for all major surgical procedures and for each of the subspecialties and fed back to each hospital, together with de-identified benchmark data from all institutions for comparison. A central committee annually reviews the data, commends low outliers, and issues warnings to high outliers. Recurrent high outlier status leads to review by regional authorities and, when indicated, site visits to assist hospitals in identifying and remedying deficiencies. Since inception of NSQIP, data for more than 1 million cases have been entered into the national database.

Over a ten-year period, 1991-2000, after implementation of NSQIP, surgical mortality decreased by 27% and complications by 45% (16). Programme leaders attribute most of these reductions to changes made by the hospitals in response to data feedback. The total cost of the program is US$ 4 million annually, approximately US$ 12 per case. The savings from reduced mortality and complications are several multiples of this expense; thus there is a net saving with this method.

The success of NSQIP in reducing adverse events and mortality can be attributed to five factors: (i) data collection is automatic part of the daily routine for all patients, not just those with complications; (ii) designated trained individuals are responsible for data collection; (iii) results are risk-adjusted; (iv) results are fed back to hospitals as site-specific data with peer hospital comparisons; (v) outcomes are monitored

by a central oversight authority with the power to conduct site visits and require changes. After initial resistance, these systems have been well-accepted by physicians and hospitals.

Routine data collection bodes well for ultimately replacing reporting as the primary source of safety information in the future. For highly developed health-care systems that have fully electronic medical records, automated data collection and analysis can provide continuous monitoring of quality and safety at a fraction of the cost of a reporting system. Similarly, automatic feed of data to a central authority (as in the Veterans Health system) can occur rapidly and inexpensively. In such a system "reporting" would be much less important, and full attention could be given to analysis and focused investigation of key events uncovered by the data analysis.

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5. NATIONAL REPORTING SYSTEMS

Key messages

- **Existing national reporting systems exhibit great variation in sponsorship, support, participation, and function.**
- **All of these reporting systems aim to improve patient safety.**
- **Reporting to most national systems is voluntary.**
- **A major issue for all reporting systems, public or private, mandatory or voluntary, is confidentiality.**

Existing national reporting systems exhibit great variation in sponsorship, support, participation, and function. Some, such as the National Reporting and Learning System (NRLS) in England and Wales, and those of Denmark, the Czech Republic, and Sweden were developed by governmental agencies to provide information to improve patient safety. Others, such as the Australian Incident Monitoring System (AIMS) sponsored by the Australia Patient Safety Foundation and the JCAHO Sentinel Events Reporting System, have been developed within the private or non-government sector.

All of these reporting systems aim to improve patient safety. However, their ability to do that varies considerably according to the sophistication of the analyses and the vigour with which efforts are pursued to turn insights into changes in practice. Patient safety is a relatively new concern for most governments. Not surprisingly, many still do not have a large cadre devoted to advancing safety or resources to carry out the plans they do make. A number of Member States have no current governmental initiatives in safety and no reporting system.

Reporting to most national systems is voluntary. However, systems in the Czech Republic and Slovenia require hospitals to report, and reporting of some especially serious events is required in the Netherlands, Japan, and other systems as well (see below for details).

Voluntary systems invite a professional ethic of participation in continuous learning and prevention, encouraged by acknowledgement and the reward of visible change. Experience from industries outside of health care, particularly aviation, as well as from some long-standing health-care reporting systems, for example, the Institute for Safe Medication Practice, shows that reporting systems are more likely to be successful if those reporting do not need to worry about adverse consequences to themselves or others.

A major issue for all reporting systems, public or private, mandatory or voluntary, is confidentiality. There is broad agreement across many systems that patients' and caregivers' names should not be disclosed, and these are protected by almost all systems. However there is much less agreement on whether the public should have access to hospital-level information.

Governmental health-care systems have a fiduciary responsibility to the public to ensure reasonable levels of safe care in health-care organizations, and reporting systems are one mechanism for discharging that responsibility.

Although accountability does not require release of all information, some form of public disclosure of adverse incidents seems indicated. Some systems make the events themselves available to the public; others disclose results of investigations or summary reports. Another option is to provide public notice of the occurrence of a serious event and of the actions taken in response by the institution and the government. Some agencies issue annual reports that summarize events and actions taken.

Types of patient safety reporting systems

The following information has been provided by representatives of reporting systems from across the world as a result of a survey undertaken for these guidelines.

Czech Republic

Type of reporting system: The Czech Republic has a mandatory reporting system. Voluntary reporting has also been in place for two years in 50 hospitals, and a national pilot project has been launched for voluntary reporting.

What is reported: Reportable events include nosocomial infections, adverse drug reactions, transfusion reactions, and medical equipment failures.

Who reports: Health care professionals.

How they report: Reports yield simple statistics of adverse events.

Analysis: Information is aggregated at different levels, including by hospital, medical specialization, region, and the republic. Analysis of sentinel event reporting in the field of acute hospital care launched in 2004; a similar project has been launched in long term care.

Response, dissemination and application of results: Reports are not accessible to the public.

Denmark

Type of reporting system: The Act on Patient Safety in the Danish Health Care System came into force January 1, 2004. The objective of the Act is to improve patient safety within the Danish health care system. The law obligates health care professionals to report specified adverse events to a national database. To support learning, this national mandatory system is sharply separated from the system of sanctions.

What is reported: Reportable adverse events are "events resulting from treatment by or stay in a hospital and not from the illness of a patient, if such event is at the same time either harmful, or could have been harmful had it not been avoided beforehand, or if the event did not occur for other reasons. Adverse events shall comprise events and errors known and unknown" Surgical events and medication errors, including close calls, must be reported.

Who reports: Healthcare professionals who become aware of an adverse event in connection with a patient's treatment or hospital stay are required to report the event.

How they report: Health care professionals report to the national database. Reports are automatically forwarded to the county where the event occurred and county councils record, analyse, and de-identify the reports. Lastly, reports are forwarded to the National Board of Health, which maintains a national register of adverse events.

Analysis: Although there are no national requirements for analysis, there is general use of the Safety Assessment Code (SAC) score. Adverse events with less serious SAC scores are acted upon locally, whereas serious adverse events (SAC score of three) prompt a root cause analysis.

Response, dissemination and application of results: Hospital owners are obligated by the Act on Patient Safety to act on reports, while the National Board of Health is charged with dissemination of lessons learnt. The National Board of Health issues alerts in the form of regular newsletters, in addition to an annual report.

Further information: www.patientsikkerhed.dk

England and Wales

Type of reporting system: The National Reporting and Learning System (NRLS) has been developed by the National Patient Safety Agency (NPSA) to promote an open reporting culture and a process for learning from adverse events. The purpose of the NRLS is to elicit reports of patient safety incidents, identify themes and patterns in the types of incidents being reported including major systems failures, and to develop and promote implementation of solutions.

The NRLS was launched in February 2004. As of July 2005, 548 NHS organizations have successfully connected to NRLS (90% of the total number).

What is reported: Patient safety incidents to be reported are defined as "any unintended or unexpected incident that could have or did lead to harm for one or more patients receiving NHS-funded healthcare". Reports are anonymous, although a NHS Trust identifier is maintained; if staff or patient names are provided, they are removed before data are entered in the database.

Who reports: Any health care staff member can report a patient safety incident to the NRLS. The NPSA receives reports from NHS Trusts who in turn encourage reporting of patient safety incidents from each organization. The Trusts can be Acute, Primary Care, Mental Health or Ambulance Service oriented. Participation by health care services is voluntary.

How they report: Health care organizations with electronic risk management systems can use a technical link to submit reports directly from this local system into the NRLS. The NPSA has worked with local risk management software vendors to establish compatibility and interfaces. The objective is to have reports that are already collected for local use forwarded seamlessly to the national repository, therefore avoiding any duplication of data entry. Data are submitted to the NRLS at a rate of around 10,000 reports a week. The NSPA has worked with every Trust to 'map' its dataset to that of the NRLS (1).

The NPSA has also developed an electronic reporting form, the 'eForm', for use by organizations without compatible commercial risk management system software or for reports submitted independently of an organization's risk management system. The NRLS provides a detailed report form that guides the user through multiple question categories with coded options defining categories of where, when how, and what occurred. Brief sections for narratives are embedded throughout the form.

Patients and carers can telephone reports to the relevant Trusts' NHS Patient Advice and Liaison Service. Staff can also send in reports directly and plans exist to enable patients and from 2006 carers to report via an eForm.

Analysis: After data cleansing (the removal of identifying information), the NPSA database supports the identification of trends based on the specific data elements defined in the reporting formats. Standardized data are extracted that include the 'when and where', level of patient harm, patient characteristics, and contributing factors.

Adverse events are categorized into classes such as a medication event; these are further broken down into descriptors such as wrong quantity, wrong route, etc. The report form allows for narrative throughout, but the data provided in the structured, standardized format, can be automatically entered in the database and correlated to identify trends and relationships among the events and causes.

Reports are aggregated and analysed with expert clinical input to help understand the frequency of types of patient safety incidents, patterns and trends and underlying contributory factors. Investigation of reports submitted locally remains the responsibility of the local organizations. The NPSA does not investigate individual incidents or become involved in discipline or performance management.

Response, dissemination and application of results: Lessons learnt from NRLS are disseminated through the publication of NPSA Patient Safety Observatory reports and through feedback to reporting organizations on incident trends and solutions. Lessons learned from the NRLS feeds into the NPSA work on safety solutions.

Incident reports are not accessible to the public, but NHS Trusts may (and do) make information available at their discretion. The NPSA also provides root cause analysis training.

Further information: www.npsa.nhs.uk

The Netherlands

Type of reporting system: Non-punitive, voluntary reporting systems for adverse events are in place within most hospitals and other health care organizations. A mandatory system also exists for reporting serious adverse events (with permanent injury or death as result) which is monitored by the Health Care Inspectorate. There is considerable under-reporting.

What is reported: There is a legal requirement that serious adverse events are reported to the Health Care Inspectorate; adverse events resulting in persistent patient injury or death are reported, as well as suicides and acts of sexual harassment. Medical equipment failures are reported by manufacturers in accordance with legal European obligations.

Who reports: Voluntary reporting is conducted by anonymous sources, hospital or health care organizations, other health care organizations, patients, health care professionals and members of the public. Mandatory reporting is conducted by hospital or healthcare organizations, other health care organizations or by licensing or disciplinary actions.

How they report: Reports can be submitted by mail, fax, or phone.

Analysis: Data classification among the hospital systems is not standardized, meaning no national aggregation of data. The national mandatory system collates data.

As part of a regulatory response all hospitals are required to investigate serious events and redesign systems.

Response, dissemination and application of results: Following receipt of reports by the agency, most reports are investigated; receive analysis of incident causation and feedback to the reporter. The classification and collation of data is not solid and, therefore, may be unreliable. The Health Care Inspectorate received 2716 reports in 2003; average annual number of reports 3000. Committees for the investigation of adverse events in individual health care institutions are required to make an annual report. The Health Care Inspectorate produces an annual report of summary data which is made publicly available.

Further information: www.minvws.nl

Ireland

Type of reporting system: The Republic of Ireland established enterprise liability under a Clinical Indemnity Scheme (CIS) in 2002 to promote safe patient care, to reduce the number of claims and to manage claims in a timely fashion. A secure web based Clinical Incident Reporting System is being rolled out nationally.

What is reported: Reportable adverse incidents include "events arising as consequence of provision of, or failure to provide clinical care that results in injury, disease, disability, death or prolonged hospital stay for the patient" and "near misses".

Who reports: All enterprises covered by the CIS are required to report on a mandatory basis, all adverse clinical events and "near misses".

How they report: Paper reports are submitted to local risk management personnel. These data are then transmitted electronically to the Clinical Indemnity Scheme central database via a secure web based system (STARSweb).

Analysis: STARSweb enables aggregated statistical analysis and supports detection of trends both at the enterprise and national level.

Response, dissemination and application of results: Lessons learnt will be disseminated through quarterly newsletters, topic-based seminars, and via a regularly updated website.

Further information: www.dohc.ie

Slovenia

Type of reporting system: A voluntary national reporting system for sentinel events was established in 2002, similar to that developed by the Joint Commission on Accreditation of Healthcare Organizations in the United States.

What is reported: Sentinel events reported include: unexpected death; major permanent loss of function; suicide of a patient while in the hospital; discharge of a newborn infant to a wrong family; hemolytic transfusion reaction following administration of blood or blood products because of the incompatibility of major blood groups; surgery on a wrong patient or body part; and neglect which has a possible characteristic of a criminal offence.

Who reports: Hospitals

How they report: Reported information is analyzed at the Ministry of Health, who also provide an initial feedback to the health care organization where the error occurred.

Response, dissemination and application of results: Reports are accessible to the public as anonymous summaries disseminated via the internet.

Sweden

Type of reporting system: The Swedish healthcare law of 1997 requires every medical institution to have a quality system; most medical institutions have implemented different forms of quality systems, which are regulated by Statutes issued by the National Board of Health and Welfare (NBHW). The reporting and learning system is part of a regulatory response that requires hospitals to investigate serious events and redesign systems.

What is reported: Events resulting in unanticipated serious injury or disease or risk thereof are reported; this covers adverse events, near misses, equipment failures, suicide and other hazardous events.

Who reports: Reports are received from hospital and health care organizations and health care professionals.

Hospitals, heath care organization, licensing and disciplinary bodies are required to report adverse events to their nearest superior offices. Patients, health care professionals and members of the public voluntarily report events.

How they report: Reporting is done in paper format via mail or fax. The National Board of Health and Welfare receives reports; approximately 1100 mandatory and 2400 voluntary reports are received annually. The board investigates most reports and provides an analysis of incident causation; in all cases feedback is provided to the reporter.

Analysis: Regional supervisory units of the NBHW receive reports and carry out inspections. In a limited number of cases reports are sent to the Medical responsibility board (HSAN), where certified health care personnel may be subject to disciplinary actions.

Response, dissemination and application of results: The Board issues recommendations to influence statutes in order to promote patient safety.

All reports to the NBHW are accessible to the public, but all personal data about any patients involved are confidential.

United States of America

Type of reporting system: The United States does not have a national governmental reporting system, but 21 of the 50 state governments operate mandatory reporting systems. Many of these have been in place for decades. All 21 mandate reporting of unexpected deaths, and several mandate reporting of wrong-site surgery. Beyond this, definitions of reportable events vary widely. Reports of serious events may trigger on-site investigations by state health departments. Less serious reports usually do not elicit a visible response. States cite insufficient staff as a barrier to follow-up, education, consultation, and oversight. Some degree of public disclosure occurs in all states, but the degrees of protection and methods of public release of information vary considerably.

Private and non-government initiated systems

Australia - the Australian Incident Monitoring System (AIMS)

Type of reporting system: The Australian Incident Monitoring System (AIMS) was founded in 1993, as an extension of the Anesthesia AIMS, formed in 1987. The objectives of AIMS is to promote learning of new hazards, trends, risk factors and contributing factors.

What is reported: AIMS is designed to receive a wide range of events, including pre-defined "Sentinel" events, all adverse events, near misses, equipment failures, new hazards, and specific events such as suicide and abduction. AIMS can accept and classify incident information from any source including incident reports, sentinel events, root cause analysis, coroner's findings, consumer reports, and morbidity and mortality reviews.

Deliberately unsafe, abusive or criminal acts are not reported to AIMS but to mandatory reporting agencies.

Who reports: Reports are accepted from all sources, including hospitals, outpatient facilities, emergency departments, aged care (long term care), community care, professionals, patients and families, and anonymous sources.

The system is voluntary and confidential. By law, AIMS databases have been designated a formal quality assurance activity. This status confers protection from legal disclosure; revealing or disseminating individually-identifying information that becomes known solely as a result of safety and quality activities is a criminal offense.

Databases reside in a fully secure location with strictly limited access.

How they report: A single system (incorporating different forms) is used for all incidents. Reports are submitted by paper, electronically, or by phone.

Analysis: The classification system in AIMS is perhaps the most highly developed of any known reporting system, comprising more than a million permutations of terms to describe an incident or adverse event. The purpose of the classification process is to translate information about an incident into a common language and create an electronic record that can be compared with other records and can be analysed as part of a larger set of data. The latest classification is based on the Professor Runciman's Generic Reference Model (GRM). The GRM is based on the Reason model of complex system failure (2).

The GRM has the components contributing factors (environmental, organizational, human, subject of incident, agents), details of the incident (type, component, person involved, timing of the incident, timing of detection, method of detection, preventability), factors minimizing or aggravating outcomes or consequences, and outcomes for the patient and organization.

The GRM is implemented via Healthcare Incident Types (HITs). HITs are a series of cascading, hierarchically based questions and answers designed to "de-construct" the information in a way that facilitates subsequent analysis and learning.

AIMS allows the reporter to deconstruct an incident into a very detailed data set that can be used for analysis, aggregation, and trending. Owing to the rich "natural categories" in the classification scheme, interrelationships among event types, risk factors, and contributing causes can be probed.

A specific data module allows the user to develop a risk matrix to determine the severity of risk. Statistical correlations among the many elements in each category are explored to identify meaningful relationships and provide analysis that can generate insights into the overall systems of care.

AIMS has a hierarchically-based, completely customizable organization tree. All wards, departments, divisions, hospitals, health services, states or territories and nations can be represented. The organization tree has the potential for 13 levels.

Incidents can be analysed at the organization level and below at which the analyst has security rights (security constraints prevent analysts querying incidents above the organization node where they security privileges).The organization tree structure allows the whole spectrum of analysis from local management of problems to aggregated analysis at a national level. The AIMS system is well equipped to provide reports and queries on any term in the database, which makes it possible for institutions or departments to compare data.

Response, dissemination and application of results: The Australian Patient Safety Foundation provides newsletters, publications, and advice at a system level. The Health Departments who use AIMS also distribute information in the form of newsletters and publications.

Putting the information, trends, and recommendations into action is the responsibility of reporting facilities. Health care facilities and organizations are able to access AIMS findings from problem-specific task forces to lead patient safety initiatives.

Further information: www.apsf.net.au

Japan

Type of reporting system: In Japan, hospitals are mandated by the Ministry of Health, Labour and Welfare to have internal reporting systems. The Japan Council for Quality Health Care collects voluntary incident reports and implemented a national reporting system in 2004. Reporting to the new system is mandatory for teaching hospitals, voluntary for others

Reporting systems exist on three levels; hospital or health facility; voluntary system in several different forms such as accreditation body for hospitals and a research group, and at national level which is mandatory.

What is reported: Patient injuries, sometimes referred to as adverse events are reported along with near-misses and equipment failures.

Who reports: Reports are received from hospitals or health care organizations.

How they report: Any hospital or healthcare organization can voluntarily report to accrediting bodies. There is a mandatory requirement to report to the Japan Council for Quality Health Care. Information is reported electronically.

Analysis: The Agency will provide analysis of incident causation and feedback of analysis to the reporter. The data are classified and summary results are disseminated to healthcare providers and to the public.

Response, dissemination and application of results: Cases deemed particularly important are evaluated individually. Otherwise, reports are aggregated for statistical analysis (further details not available). The Japan Council for Quality Health Care produces summary reports of events and disseminates them to healthcare providers and to the public.

U.S.A. - Institute for Safe Medication Practices (ISMP)

Type of reporting system: ISMP is a national, confidential medication error reporting system. that distributes hazard alerts and other medication safety information to 600,000 providers every other week.

What is reported: ISMP is a focused reporting system for adverse drug events and hazards in medication delivery and management.

Who reports: Reports are accepted from health care professionals, organizations, or patients.

How they report: Reports from organizations or professionals can be submitted online, electronically, by telephone, mail, or fax.

Analysis: Over half of reporters are called back to elicit details about hazardous medication packaging or devices information of brand name, model number, or a photograph illustrating the problem This detailed information is extracted to enable specific, direct and immediate influence on hazard reduction. Medication information is classified according to 10 key elements. Hazard identification is done by human expertise; a group of experts observes recurrent reports, works closely together, and applies their knowledge to appreciate the urgency of a problem. Rapid turnaround permits numerous hazard alerts, so that an overall analysis for prioritization is unwarranted.

Response, dissemination and application of results: ISMP is engaged in numerous actions to support hazard reduction, such as promoting maximum dose statements on chemotherapy vial caps, elimination of pre-filled syringes for hazardous cardiac medications, identification and reduction of hazardous medical abbreviations among providers and pharmaceutical advertisements, and several other collaborations with pharmaceutical companies, device manufacturers, and the United States FDA.

Further information: www.ismp.org

U.S.A - Joint Commission on Accreditation of Healthcare Organizations (JCAHO)

Type of reporting system: The Joint Commission on Accreditation of Healthcare Organizations implemented a Sentinel Event Reporting System in 1996. The system is designed to facilitate identification and learning among healthcare organizations of sentinel events and their prevention strategies. The system is voluntary and confidential. Accreditation status is not penalized for any organization that reports an error and applies due process to its future prevention.

What is reported: Reported sentinel events include: event has resulted in an unanticipated death or major permanent loss of function, not related to the natural course of the patient's illness or underlying condition, or the event is one of the following (even if the outcome was not death or major permanent loss of function unrelated to the natural course of the patient's illness or underlying condition): suicide of any individual receiving care, treatment or services in staffed around-the-clock care setting or within 72 hours of discharge; unanticipated death of a full-term infant; abduction of any individual receiving care, treatment or services; discharge of an infant to the wrong family; rape; hemolytic transfusion reaction involving administration of blood or blood products having major blood group incompatibilities; surgery on the wrong individual or wrong body part; unintended retention of a foreign object in an individual after surgery or other procedure.

Who reports:Reports are received from health care organizations and other sources such as media, complaints and the State Health Department.

How they report:Any accredited healthcare organization may submit reports.

Analysis: JCAHO require organizations to conduct a root cause analysis accompanied by an action plan. JCAHO also require access to review the organization's response to the sentinel event (which may or may not include actually reviewing the RCA). Guidance on conducting root cause analysis is offered by JCAHO on their website or upon request. Although reporting is voluntary, providing a root cause analysis is required.

Before the data describing the event, its root causes, and risk reduction strategies can be accepted into the database, the organization's response must meet certain defined criteria for acceptability.

Response, dissemination and application of results: Using their database and collaborating with experts, JCAHO periodically chooses a reported event type and develops a Sentinel Event Alert describing the events, causes, and strategies gathered from organizations for prevention. Publications began in 1998; to date 34 issues of Sentinel Event Alert have been published.

The individual organization's action plan is monitored by the JCAHO in a manner similar to the monitoring of corrective actions of other quality concerns. On a broader scale, hospitals' responses to the "Sentinel Event Alerts" are considered

during accreditation survey. The JCAHO have instituted National Patient Safety Goals as an influential derivative of the Sentinel Event reporting process.

Further information: www.jcaho.org

U.S.A - United States Pharmacopoeia MedMARx[SM]

Type of reporting system: MedMARx[SM] is a voluntary system designed to identify hazards and systems vulnerabilities, identify best practices, and gather information that will support the standard-setting activities of USP.

What is reported: Adverse drug events, near misses, and errors can all be submitted to MedMARx[SM].

Who reports: MedMARx[SM] accepts reports from healthcare professionals,organizations, and patients. Since its introduction in 1998, over 900 healthcare facilities have contributed over 630,000 medication error reports (Personal communication with J.Silverstone National Patient Safety Foundation email listserve, editor. 4-20-2004). Currently, they receive approximately 20,000 reports each month (Personal communication with D. Cousins 5-19-2004) or about 20 per month for each of their 900 healthcare facilities.

How they report: Reports can be submitted directly through a web-based portal, submitted electronically, or by telephone, mail, and fax.

Analysis: Reports are entered into a database that can be searched and used to count, sort, and correlate events.

Response, dissemination and application of results: USP analyzes the errors in MedMARx[SM] and provides an annual summary report. The database gathered by the USP is provided to the US Food and Drug Administration. A research partnership is underway with the Agency for Healthcare Research and Quality (AHRQ) to study the data for further improvement opportunities.

Further information: www.medmarx.com

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6. CHARACTERISTICS OF SUCCESSFUL REPORTING SYSTEMS

Key messages

A successful reporting and learning system to enhance patient safety should have the following characteristics:

- **reporting is safe for the individuals who report;**
- **reporting leads to a constructive response;**
- **expertise and adequate financial resources are available to allow for meaningful analysis of reports;**
- **the reporting system must be capable of disseminating information on hazards and recommendations for changes.**

The ultimate measure of the success of a reporting system is whether the information it yields is used appropriately to improve patient safety. How that is done varies greatly according to the aims of its sponsor. While both learning and accountability systems seek to improve learning from mistakes, the fiduciary objectives of the latter impose an additional constraint: satisfying the public's interest in making sure that known mechanisms for injury prevention are being used (rules and safe practices) and that new hazards are promptly addressed when they are uncovered. This may require some departure from the following concepts, particularly regarding confidentiality and independence.

Successful patient safety reporting systems have the following characteristics:

- reporting must be safe for the individuals who report;
- reporting is only of value if it leads to a constructive response, and meaningful analysis;
- learning requires expertise and adequate financial resources. The agency that receives reports must be capable of disseminating information and making recommendations for changes, and informing the development of solutions.

Table One lists the characteristics that have been identified by various authors as essential to the success of any reporting systems concerned with patient safety (1-4). Many of these characteristics are derived from long experience both in health care (for example, the Institute for Safe Medication Practice) and in other industries, particularly aviation. These essential characteristics are discussed below.

Non-punitive. The most important characteristic for success of a patient safety reporting system is that it must be non-punitive. Neither reporters nor others involved in the incidents can be punished as a result of reporting. For public systems, this requirement is the most difficult to achieve, since the public often assumes an individual is to blame, and there can be strong pressure to punish the "culprit". While perhaps temporarily emotionally satisfying, this approach is doomed to fail. People will not report any errors they can hide. It is important for national systems to protect reporters from blame. The best way to do this is by keeping the reports confidential.

Confidential. The identities of the patient and reporter must never be revealed to any third party. At the institutional level, confidentiality also refers to not making public specific information that can be used in litigation. Although, historically, breach of confidentiality has not been a problem in public or private systems, concern about disclosure is a major factor inhibiting reporting for many voluntary reporting programmes (5).

Independent. The reporting system must be independent of any authority with the power to punish the reporter or organization with a stake in the outcome. Maintaining a "firewall" between the reporting agency and the disciplinary agency in a governmental system can be difficult, but it is essential if trust in reporting is to be maintained.

Expert analysis. Reports must be evaluated by experts who understand the clinical circumstances under which the incidents occur and who are trained to recognize underlying systems causes. While it seems obvious that collecting data and not analysing it is of little value, the most common failure of governmentally run reporting systems is to require reporting but not to provide the resources needed to analyse the reports. Huge numbers of reports are collected only to sit in boxes or on computers. Expertise is a major, and essential, resource requirement for any reporting system.

Credible. The combination of independence and the use of content experts for analysis is necessary if recommendations are to be accepted and acted upon.

Timely. Reports must be analysed without delay, and recommendations must be promptly disseminated to those who need to know. When serious hazards are identified, notification should take place rapidly. For example, the Institute for Safe Medication Practice issues prompt alerts through its regular publication when new hazards in drugs are discovered.

Systems-oriented. Recommendations should focus on changes in systems, processes or products, rather than being targeted at individual performance. This is a cardinal principle of safety that must be reinforced by the nature of recommendations that come from any reporting system. It is based on the concept that even an apparently egregious individual error results from systems defects, and will recur with another person at another time if those systems defects are not remedied.

Responsive. For recommendations to result in widespread systems changes, the organization receiving reports must be capable of making and disseminating effective recommendations, and target organizations must make a commitment to implement recommendations. A good example is the National Reporting and Learning System in England and Wales which allows the National Patient Safety Agency to develop new solutions that are disseminated throughout the system.

Table 1 Characteristics of Successful Reporting Systems (7)

Non-punitive	Reporters are free from fear of retaliation against themselves or punishment of others as a result of reporting.
Confidential	The identities of the patient, reporter, and institution are never revealed.
Independent	The reporting system is independent of any authority with power to punish the reporter or the organization.
Expert analysis	Reports are evaluated by experts who understand the clinical circumstances and are trained to recognize underlying systems causes.
Timely	Reports are analysed promptly and recommendations are rapidly disseminated to those who need to know, especially when serious hazards are identified.
Systems-oriented	Recommendations focus on changes in systems, processes, or products, rather than being targeted at individual performance.
Responsive	The agency that receives reports is capable of disseminating recommendations. Participating organizations commit to implementing recommendations whenever possible.

Several of these characteristics are included among the attributes that Runciman has proposed for national reporting and learning systems (6):

- an independent organization to coordinate patient safety surveillance;
- agreed frameworks for patient safety and surveillance systems;
- common, agreed standards and terminology;
- a single, clinically useful classification for things that go wrong in health care;
- a national repository for information covering all of health care from all available sources;
- mechanisms for setting priorities at local, national and international levels;
- a just system which caters for the rights of patients, society, and health-care practitioners and facilities;
- separate processes for accountability and "systems learnings";
- the right to anonymity and legal privilege for reporters;
- systems for rapid feedback and evidence of action;
- mechanisms for involving and informing all stakeholders.

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7. REQUIREMENTS FOR A NATIONAL ADVERSE EVENT REPORTING AND LEARNING SYSTEM

Key messages

Certain capacities are needed for all reporting systems, whether simple or complex. These are:

- **clear objectives;**
- **clarity about who should report;**
- **clarity about what gets reported;**
- **mechanisms for receiving reports and managing the data;**
- **expertise for analysis;**
- **capacity to respond to reports;**
- **a method for classifying and making sense of reported events;**
- **the capacity to disseminate findings;**
- **technical infrastructure and data security.**

Before deciding whether to establish a national adverse event reporting and learning system, states should carefully consider (i) what the objectives of the system are (ii) whether they can develop the capacity to respond to reports; and (iii) the resources that will be required. It is also important to decide the scope of what is to be reported and the data to be collected.

Appendix 2 provides a quick reference checklist of issues to consider in developing a reporting system.

Objectives

Ideally, the objectives of a reporting system emerge from the perceived needs of a patient safety programme. Reporting is a tool for obtaining safety information. A national reporting system, therefore, can usefully be regarded as a tool to advance public policy concerning patient safety. It should be an extension of a programme

of quality improvement and error prevention. To be effective, learnings from the analysis of reports must feed into a mechanism for developing and disseminating changes in policy and practice that improve safety.

If the commitment to improvement is weak, or if there is no infrastructure to carry out implementation of changes, such as an agency charged with improving safety, a reporting system will be of little value. Stating it simply, it is more important to develop a response system than a reporting system. If there is a commitment to improvement of patient safety and some infrastructure, but resources are scant, alternative methods of identifying problem areas may be preferable (See Section 4).

Capacity to respond

Certain capacities are needed for all reporting systems, whether simple or complex. These are a mechanism for receiving the reports and managing the data, some capacity to get additional information, a technical infrastructure, a method for classifying events, expertise for analysis, and the capacity to disseminate findings.

Mechanism for collecting reports and database management

The optimal process for receiving, inputting, analysing, and disseminating reports will vary according to the specific objectives and focus of an individual reporting system. For example, a structured input can help with analysis, whereas story telling captures rich detail and context. Personal contact from phone calls or reading written reports engages the receiver with each report, whereas direct electronic transmission facilitates ease of use and direct database entry. Keeping in mind the essential objectives of the reporting system and considering available types of technical support and overall resources will help developers determine which methods are most suitable.

When reports are received by mail, phone, or fax, front-line staff must have a process for the initial sorting and triage of reports. Staff may be called upon to judge whether a report can be entered directly into the database, or requires forwarding to an internal expert for further understanding.

One advantage of reports being received by individuals (as opposed to automatic data transfer) is that staff may recognize that reports of certain types of events have recurred and then query the database to confirm a trend. Reporting systems that receive reports in this fashion require resources to perform data entry and manage the integrity of the database for organizing identifying information about each report.

Capacity to investigate

Even with simple systems that focus primarily on recognizing hazards, resources should be available to support follow-up on reports, provide feedback to the reporter, and conduct at least a limited investigation when indicated. More sophisticated systems will have the capacity to find out more about the context in which the event occurred and conduct a systems analysis or other process for understanding the clinical issues and systems flaws underlying the event. This may also require further discussions with the reporter or an on-site investigation. Experts who perform this function must be sufficiently familiar both with the clinical context and with systems principles to identify potential themes and extract the essential learnings from the event.

Technical infrastructure

The technical infrastructure required to support reporting systems may be very simple or quite sophisticated. Reporting systems that use phone, mail or fax require as a minimum an efficient method for communicating with internal or external experts, tracking the database and generating reports. Web-based systems offer ease of use to reporters and also eliminate the need for staff to do data entry. The technical infrastructure to enable entered reports to be downloaded into a database is most readily achieved with standardized data fields.

Finally, all systems must provide technical support to users who may require assistance, whether with paper forms or on-line reporting functions.

Method for classifying events

There are three key factors in determining what classification system should be used:

- the purpose of the reporting system, and thus the type of information desired and how the classification scheme will facilitate the purpose for which data are being collected;
- the nature of the data available since underlying systems causes cannot be included in a classification scheme if those data are not reported;
- Resources, bearing in mind that elaborate classification systems that require substantial expertise can be expensive.

Reporting systems with predefined events may have a minimal classification scheme that sorts events into simple categories. Such a scheme yields a count and possibly trends but provides little opportunity for further analysis.

A more sophisticated classification scheme will include categories such as causal factors, severity, probability of recurrence, and type of recovery. An ideal system will also obtain, and classify, information about contributing factors (see Section 3 for a detailed discussion of classification systems).

Expert analysis

Whether analysing relatively simple reports to identify and understand new hazards, or searching for common underlying contributing factors in serious adverse events, all reporting systems need experts who understand the content and context of reported events. Experts determine whether reports are for identifying trends only, require follow-up with the reporter for further information, should trigger an on-site investigation, or herald an emerging hazard that warrants alerting the health-care organizations.

To provide meaningful recommendations, it is necessary to have experts who understand the practice concerns, clinical significance, systems issues, and potential preventive measures for the problems raised by the reports. Ultimately, it is human experts who must translate the knowledge gleaned from aggregated reports into meaningful recommendations for action to improve care.

Capacity to disseminate findings and recommendations

To fulfill their mission, reporting systems must communicate back to the community from which the reports are received. Reports, newsletters, communications, or alerts distill the meaning of aggregated reports into meaningful themes, identify proposed actions to prevent harm, inform policy-makers of issues, broadcast solutions and best practices, or alert pharmaceutical companies, device manufacturers, or health-care providers to new hazards. This requires staff to write reports and a mechanism to disseminate reports, such as large-scale mailings, press releases, newsletters, or electronic bulletins.

At a higher level, findings from the reporting system inform new safety initiatives that are generated and implemented by the appropriate authority. The National Reporting and Learning System of England and Wales, for example, feeds information and recommendations to the National Patient Safety Agency, which develops initiatives and campaigns to implement solutions.

While ultimately the effectiveness of a reporting system is measured by improvements in clinical outcomes, an intermediary measure is the number of recommendations generated from analyses of reports.

Security issues

Whereas reports within a health-care organization often have rich detail and usually contain information that makes it possible to identify the people concerned, it is important that such information is removed from external reports and de-identified to protect patients, providers and reporters. Confidentiality protection against unauthorized access must be implemented with a data security system. This may include a process for de-identifying reports upon their receipt or after a follow-up

investigation has occurred. A lock box or "firewall" may be indicated to protect against inadvertent data sharing with other parties or agencies. Data encryption methods are essential for web-based reporting systems. Data security systems also should have a mechanism for identifying breaches of security.

8. RECOMMENDATIONS TO WHO MEMBER STATES

1. Adverse event reporting and learning systems should have as their main objective the improvement of patient safety through the identification of errors and hazards which may warrant further analysis and investigation in order to identify underlying systems factors.

2. When designing adverse event reporting and learning systems, the responsible parties should clearly set out:

- the objectives of the system
- who should report
- what gets reported
- mechanisms for receiving reports and managing the data
- sources of expertise for analysis
- the response to reports
- methods for classifying and making sense of reported events
- ways to disseminate findings
- technical infrastructure and data security.

3. Health-care workers and organizations should be encouraged to report a wide range of safety information and events.

4. Health-care workers who report adverse events, near misses and other safety concerns should not be punished as a result of reporting.

5. Reporting systems should be independent of any authority with power to punish the reporter.

6. The identities of reporters should not normally be disclosed to third parties.

7. Reported events should be analysed in a timely way.

8. Reported events should be analysed by experts who understand the clinical circumstances and care processes involved and who are trained to recognize underlying systems causes.

9. The entity that receives reports should be capable of making and disseminating recommendations. Participating organizations should agree to implement recommendations wherever possible.

10. Recommendations for preventative strategies should be rapidly disseminated, especially when serious hazards are identified.

APPENDIX 1
EXCERPT FROM INSTITUTE OF MEDICINE REPORT TO ERR IS HUMAN

Why Do Errors Happen?

The common initial reaction when an error occurs is to find and blame someone. However, even apparently single events or errors are due most often to the convergence of multiple contributing factors. Blaming an individual does not change these factors and the same error is likely to recur. Preventing errors and improving safety for patients require a systems approach in order to modify the conditions that contribute to errors. People working in health care are among the most educated and dedicated workforce in any industry. The problem is not bad people; the problem is that the system needs to be made safer.

This chapter covers two key areas. First, definitions of several key terms are offered. This is important because there is no agreed-upon terminology for talking about this issue.[1] Second, the emphasis in this chapter (and in this report generally) is about how to make systems safer; its primary focus is not on "getting rid of bad apples," or individuals with patterns of poor per-formance. The underlying assumption is that lasting and broad-based safety improvements in an industry can be brought about through a systems approach.

Finally, it should be noted that although the examples may draw more from inpatient or institutional settings, errors occur in all settings. The concepts presented in this chapter are just as applicable to ambulatory care, home care, community pharmacies, or any other setting in which health care is delivered.

This chapter uses a case study to illustrate a series of definitions and concepts in patient safety. After presentation of the case study, the chapter will define what comprises a system, how accidents occur, how human error contributes to accidents and how these elements fit into a broader concept of safety. The case study

will be referenced to illustrate several of the concepts. The next section will examine whether certain types of systems are more prone to accidents than others. Finally, after a short discussion of the study of human factors, the chapter summarizes what health care can learn from other industries about safety.

WHY DO ACCIDENTS HAPPEN?

Major accidents, such as Three Mile Island or the Challenger accident, grab people's attention and make the front page of newspapers. Because they usually affect only one individual at a time, accidents in health care delivery are less visible and dramatic than those in other industries. Except for celebrated cases, such as Betsy Lehman (the Boston Globe reporter who died from an overdose during chemotherapy) or Willie King (who had the wrong leg amputated),[2] they are rarely noticed. However, accidents are a form of information about a system.[3] They represent places in which the system failed and the breakdown resulted in harm.

The ideas in this section rely heavily upon the work of Charles Perrow and James Reason, among others. Charles Perrow's analysis of the accidentat Three Mile Island identified how systems can cause or prevent accidents.[4] James Reason extended the thinking by analyzing multiple accidents to examine the role of systems and the human contribution to accidents.[5] *"A system is a set of interdependent elements interacting to achieve a common aim. The elements may be both human and non-human (equipment, technologies, etc.)."*

Systems can be very large and far-reaching, or they can be more localized. In health care, a system can be an integrated delivery system, a centrally owned multihospital system, or a virtual system comprised of many different partners over a wide geographic area. However, an operating room or an obstetrical unit is also a type of system. Furthermore, any element in a system probably belongs to multiple systems. For example, one operating

An Illustrative Case in Patient Safety

Infusion devices are mechanical devices that administer intravenous solutions containing drugs to patients. A patient was undergoing a cardiac procedure. This patient had a tendency toward being hypertensive and this was known to the staff.

As part of the routine set-up for surgery, a nurse assembled three different infusion devices. The nurse was a new member of the team in the operating room; she had just started working at the hospital a few weeks before. The other members of the team had been working together for at least six months. The nurse was being very careful when setting up the devices because one of them was a slightly different model than she had used before.

Each infusion device administered a different medication that would be used during surgery. For each medication, the infusion device had to be programmed according to how much medication would flow into the patient (calculated as "cc's/hour"). The medications had different concentrations and each required calculation of the correct dose for that specific patient. The correct cc's/hour were programmed into the infusion devices.

The anesthesiologist, who monitors and uses the infusion devices during surgery, usually arrived for surgery while the nurse was completing her set-up of the infusion devices and was able to check them over. This particular morning, the anesthesiologist was running behind from a previous surgery. When he arrived in the operating room, the rest of the team was ready to start. The anesthesiologist quickly glanced at the set-up and accepted the report as given to him by the nurse.

One of the infusion devices was started at the beginning of surgery. About halfway through the surgery, the patient's blood pressure began to rise. The anesthesiologist

room is part of a surgical department, which is part of a hospital, which is part of a larger health care delivery system. The variable size, scope, and membership of systems make them difficult to analyze and understand.

In the case study, one of the systems used during surgery is the automated, medication adminstration system, which includes the equipment, the people, their interactions with each other and with the equipment, the procedures in place, and the physical design of the surgical suite in which the equipment and people function.

When large systems fail, it is due to multiple faults that occur together in an unanticipated interaction,[6] creating a chain of events in which the faults grow and evolve.[7] Their accumulation results in an accident. "An accident is an event that involves damage to a defined system that disrupts the ongoing or future output of that system." [8]

The *Challenger* failed because of a combination of brittle O-ring seals, unexpected cold weather, reliance on the seals in the design of the boosters, and change in the roles of the contractor and NASA. Individually, no one factor caused the event, but when they came together, disaster struck. Perrow uses a DEPOSE (Design, Equipment Procedures, Operators, Supplies and materials, and Environment) framework to identify the potential sources of failures. In evaluating the environment, some researchers explicitly include organizational design and characteristics.[9]

In the case study, the accident was a breakdown in the delivery of IV medicationsduring surgery.

The complex coincidences that cause systems to fail could rarely have been foreseen by the people involved. As a result, they are reviewed only in hindsight; however, knowing the outcome of an event influences how we assess past events.[10] Hindsight bias means that things that were not seen or understood at the time of the accident seem obvious in retrospect. Hindsight bias also misleads a reviewer into simplifying the causes of an accident,

tried to counteract this by starting one of the other infusion devices that had been set up earlier. He checked the drip chamber in the intravenous (IV) tubing and did not see any drips. He checked the IV tubing and found a closed clamp, which he opened. At this point, the second device signaled an occlusion, or blockage, in the tubing by sounding an alarm and flashing an error message. The anesthesiologist found a closed clamp in this tubing as well, opened it, pressed the re-start button and the device resumed pumping without further difficulty. He returned to the first device that he had started and found that there had been a free flow of fluid and medication to the patient, resulting in an overdose. The team responded appropriately and the patient recovered without further incident.

The case was reviewed two weeks later at the hospital's "morbidity and mortality" committee meeting, where the hospital staff reviews cases that encountered a problem to identify what happened and how to avoid a recurrence.

The IV tubing had been removed from the device and discarded. The bioengineering service had checked the pump and found it to be functioning accurately. It was not possible to determine whether the tubing had been inserted incorrectly into the device, whether the infusion rate had been set incorrectly or changed while the device was in use, or whether the device had malfunctioned unexpectedly. The anesthesiologist was convinced that the tubing had been inserted incorrectly, so that when the clamp was open the fluid was able to flow freely rather than being controlled by the infusion device. The nurse felt the anesthesiologist had failed to check the infusion system adequately before turning on the devices. Neither knew whether it was possible for an infusion device to have a safety mechansim built into it that would prevent free flows from happening.

highlighting a single element as the cause and overlooking multiple contributing factors. Given that the information about an accident is spread over many participants, none of whom may have complete information,[11] hindsight bias makes it easy to arrive at a simple solution or to blame an individual, but difficult to determine what really went wrong.

Although many features of systems and accidents in other industries are also found in health care, there are important differences. In most other industries, when an accident occurs the worker and the company are directly affected. There is a saying that the pilot is always the first at the scene of an airline accident. In health care, the damage happens to a third party; the patient is harmed; the health professional or the organization, only rarely. Furthermore, harm occurs to only one patient at a time; not whole groups of patients, making the accident less visible.*

In any industry, one of the greatest contributors to accidents is human error. Perrow has estimated that, on average, 60–80 percent of accidents involve human error. There is reason to believe that this is equally true in health. An analysis of anesthesia found that human error was involved in 82 percent of preventable incidents; the remainder involved mainly equipment failure.[12] Even when equipment failure occurs, it can be exacerbated by human error.[13] However, saying that an accident is due to human error is not the same as assigning blame. Humans commit errors for a variety of expected and unexpected reasons, which are discussed in more detail in the next two sections.

Understanding Errors

The work of Reason provides a good understanding of errors. He defines an error as the failure of a planned sequence of mental or physical activities to achieve its intended outcome when these failures cannot be attributed to chance.[14] It is important to note the inclusion of "intention." According to Reason, error is not meaningful without the consideration of intention. That is, it has no meaning when applied to unintentional behaviors because errors depend on two kinds of failure, either actions do not go as intended or the intended action is not the correct one. In the first case, the desired outcome may or may not be achieved; in the second case, the desired outcome cannot be achieved.

Reason differentiates between slips or lapses and mistakes. A slip or lapse occurs when the action conducted is not what was intended. It is an error of execution. The difference between a slip and a lapse is that a slip is observable and a lapse is not.

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* *Public health has made an effort to eliminate the term, "accident," replacing it with unintentional injuries, consistent with the nomenclature of the International Classification of Diseases. However, this report is not focused specifically on injury since an accident may or may not result in injury. See Institute of Medicine, Reducing the Burden of Injury, eds. Richard J. Bonnie, Carolyn Fulco and Catharyn Liverman. Washington, D.C., National Academy Press, 1999).*

For example, turning the wrong knob on a piece of equipment would be a slip; not being able to recall something from memory is a lapse.

In a mistake, the action proceeds as planned but fails to achieve its intended outcome because the planned action was wrong. The situation might have been assessed incorrectly, and/or there could have been a lack of knowl- edge of the situation. In a mistake, the original intention is inadequate; a failure of planning is involved.

In medicine, slips, lapses, and mistakes are all serious and can potentially harm patients. For example, in medicine, a slip might be involved if the physician chooses an appropriate medication, writes 10 mg when the intention was to write 1 mg. The original intention is correct (the correct medication was chosen given the patient's condition), but the action did not proceed as planned. On the other hand, a mistake in medicine might involve selecting the wrong drug because the diagnosis is wrong. In this case, the situation was misassessed and the action planned is wrong. If the terms "slip" and "mistake" are used, it is important not to equate slip with "minor." Patients can die from slips as well as mistakes. For this report, *error is defined as the failure of a planned action to be completed as intended (e.g., error of execution) or the use of a wrong plan to achieve an aim (e.g., error of planning).* From the patient's perspective, not only should a medical intervention proceed properly and safely, it should be the correct intervention for the particular condition. This report addresses primarily the first concern, errors of execution, since they have their own epidemiology, causes, and remedies that are different from errors in planning. Subsequent reports from the Quality of Health Care in America project will consider the full range of quality-related issues, sometimes classified as overuse, underuse and misuse.[15]

Latent and Active Errors

In considering how humans contribute to error, it is important to distinguish between active and latent errors.[16] *Active errors occur at the level of the frontline operator, and their effects are felt almost immediately. This is sometimes called the sharp end.*[17] *Latent errors tend to be removed from the direct control of the operator and include things such as poor design, incorrect installation, faulty maintenance, bad management decisions, and poorly structured organizations.* These are called the blunt end. The active error is that the pilot crashed the plane. The latent error is that a previously undiscovered design malfunction caused the plane to roll unexpectedly in a way the pilot could not control and the plane crashed

In the case study, the active error was the free flow of the medication from the infusion device.

Latent errors pose the greatest threat to safety in a complex system because they are often unrecognized and have the capacity to result in multiple types of active errors. Analysis of the Challenger accident traced contributing events back nine years. In the Three Mile Island accident, latent errors were traced back two years.[18] Latent errors can be difficult for the people working in the system to notice since the errors may be hidden in the design of routine processes in computer programs or in the structure or management of the organization. People also become accustomed to design defects and learn to work around them, so they are often not recognized.

In her book about the *Challenger* explosion, Vaughan describes the "normalization of deviance" in which small changes in behavior became the norm and expanded the boundaries so that additional deviations became acceptable.[19] When deviant events become acceptable, the potential for errors is created because signals are overlooked or misinterpreted and accumulate without being noticed.

Current responses to errors tend to focus on the active errors by punishing individuals (e.g., firing or suing them), retraining or other responses aimed at preventing recurrence of the active error. Although a punitive response may be appropriate in some cases (e.g., deliberate malfeasance), it is not an effective way to prevent recurrence. Because large system failures represent latent failures coming together in unexpected ways, they appear to be unique in retrospect. Since the same mix of factors is unlikely to occur again, efforts to prevent specific active errors are not likely to make the system any safer.[20]

In our case study, a number of latent failures were present:

- *Multiple infusion devices were used in parallel during this cardiac surgery. Three devices were set up, each requiring many steps. each step in the assembly presents a possibility for failure that could disrupt the entire system.*
- *Each of the three different medications had to be programmed into the infusion device with the correct dose for that patient.*
- *Possible scheduling problems in the operating suites may have contributed to the anesthesiologist having insufficient time to check the devices before surgery.*
- *A new nurse on the team may have interrupted the "normal" flow between the team members, especially communication between the anesthesiologist and the nurse setting up the devices. There was no standardized list of checks between the nurse and anesthesiologist before starting the procedure.*
- *Training of new team members may be insufficient since the nurse found herself assembling a device that was a slightly different model. As a new employee, she may have been hesitant to ask for help or may not have known who to ask.*

Focusing on active errors lets the latent failures remain in the system, and their accumulation actually makes the system more prone to future failure. [21] Discovering and fixing latent failures, and decreasing their duration, are likely to have a greater

effect on building safer systems than efforts to minimize active errors at the point at which they occur.

In the case study, a typical response would have been to retrain the nurse on how to assemble the equipment properly. However, this would have had no effect on weaknesses in equipment design, team management and communications, scheduling problems, or orienting new staff. Thus, free flow errors would likely recur.

Understanding Safety

Most of this chapter thus far has drawn on Perrow's normal accident theory, which believes that accident are inevitable in certain systems. Al- though they may be rare, accidents are "normal" in complex, high technology industries. In contrast to studying the causes of accident and errors, other researchers have focused on the characteristics that make certain industries, such as military aircraft carriers or chemical processing, highly reliable.[22] High reliability theory believes that accidents can be prevented through good organizational design and management.[23] Characteristics of highly reliable industries include an organizational commitment to safety, high levels of redundancy in personnel and safety measures, and a strong organizational culture for continuous learning and willingness to change.[24] Correct performance and error can be viewed as "two sides of the same coin."[25] Although accidents may occur, systems can be designed to be safer so that accidents are very rare.

The National Patient Safety Foundation has defined patient safety as the avoidance, prevention and amelioration of adverse outcomes or injuries stemming from the processes of health care.[26] Safety does not reside in a person, device or department, but emerges from the interactions of components of a system. Others have specifically examined pharmaceutical safety and defined it to include maximizing therapeutic benefit, reducing risk, and eliminating harm.[27] That is, benefit relates to risk. Other experts have also defined safety as a relative concept. Brewer and Colditz suggest that the acceptability of an adverse event depends on the seriousness of the underlying illness and the availability of alternative treatments.[28] The committee's focus, however, was not on the patient's response to a treatment, but rather on the ability of a system to deliver care safely. From this perspective, the committee believes that there is a level of safety that can and should be ensured. Safety is relative only in that it continues to evolve over time and, when risks do become known, they become part of the safety requirements.

Safety is more than just the absence of errors. Safety has multiple dimensions, including the following:

- an outlook that recognizes that health care is complex and risky and that solutions are found in the broader systems context;

- a set of processes that identify, evaluate, and minimize hazards and are continuously improving, and
- an outcome that is manifested by fewer medical errors and minimized risk or hazard.[29]

For this report, safety is defined as freedom from accidental injury. This simple definition recognizes that from the patient's perspective, the primary safety goal is to prevent accidental injuries. If an environment is safe, the risk of accidents is lower. Making environments safer means looking at processes of care to reduce defects in the process or departures from the way things should have been done. Ensuring patient safety, therefore, involves the establishment of operational systems and processes that increase the reliability of patient care.

ARE SOME TYPES OF SYSTEMS MORE PRONE TO ACCIDENTS?

Accidents are more likely to happen in certain types of systems. When they do occur, they represent failures in the way systems are designed. The primary objective of systems design ought to be to make it difficult for accidents and errors to occur and to minimize damage if they do occur.[30]

Perrow characterizes systems according to two important dimensions: complexity and tight or loose coupling.[31] Systems that are more complex and tightly coupled are more prone to accidents and have to be made more reliable.[32] In Reason's words, complex and tightly coupled systems can "spring nasty surprises."[33]

In complex systems, one component of the system can interact with multiple other components, sometimes in unexpected or invisible ways. Although all systems have many parts that interact, the problem arises when one part serves multiple functions because if this part fails, all of the dependent functions fail as well. Complex systems are characterized by specialization and interdependency. Complex systems also tend to have multiple feedback loops, and to receive information indirectly, and because of specialization, there is little chance of substituting or reassigning personnel or other resources.

In contrast to complex systems, linear systems contain interactions that are expected in the usual and familiar production sequence. One component of the system interacts with the component immediately preceding it in the production process and the component following it. Linear systems tend to have segregated subsystems, few feedback loops, and easy substitutions (less specialization).

An example of complexity is the concern with year 2000 (Y2K) computer problems. A failure in one part of the system can unexpectedly interrupt other parts, and all of the interrelated processes that can be affected are not yet visible. Complexity is also the reason that changes in long-standing production processes must be made cautiously.[34] When tasks are distributed across a team, for example, many interac-

tions that are critical to the process may not be noticed until they are changed or removed.

Coupling is a mechanical term meaning that there is no slack or buffer between two items. Large systems that are tightly coupled have more timedependent processes and sequences that are more fixed (e.g., y depends on x having been done). There is often only one way to reach a goal. Compared to tightly coupled systems, loosely coupled systems can tolerate processing delays, can reorder the sequence of production, and can employ alternative methods or resources.

All systems have linear interactions; however, some systems additionally experience greater complexity. Complex interactions contribute to accidents because they can confuse operators. Tight coupling contributes to accidents because things unravel too quickly and prevent errors from being intercepted or prevent speedy recovery from an event.[35] Because of complexity and coupling, small failures can grow into large accidents.

In the case study, the medication adminstration system was both complex and tightly coupled. The complexity arises from three devices functioning simultaneously, in close proximity, and two having problems at the same time. The tight coupling arises from the steps involved in making the system work properly, from the steps required to assemble three devices, to the calculation of correct medication dosage levels, to the operation of multiple devices during surgery, to the responses when alarms start going off.

Although there are not firm assignments, Perrow considered nuclear power plants, nuclear weapons handling, and aircraft to be complex, tightly coupled systems.[36] Multiple processes are happening simultaneously, and failure in one area can interrupt another. Dams and rail transportation are considered tightly coupled because the steps in production are closely linked, but linear because there are few unexpected interactions. Universities are considered complex, but loosely coupled, since the impact of a decision in one area can likely be limited to that area.

Perrow did not classify health care as a system, but others have suggested that health care is complex and tightly coupled.[37] The activities in the typical emergency room, surgical suite, or intensive care unit exemplify complex and tightly coupled systems. Therefore, the delivery of health care services may be classified as an industry prone to accidents.[38]

Complex, tightly coupled systems have to be made more reliable.[39] One of the advantages of having systems is that it is possible to build in more defenses against failure. Systems that are more complex, tightly coupled, and are more prone to accidents can reduce the likelihood of accidents by simplifying and standardizing processes, building in redundancy, developing backup systems, and so forth.

Another aspect of making systems more reliable has to do with organizational design and team performance. Since these are part of activities within organizations, they are discussed in Chapter 8.

Conditions That Create Errors

Factors can intervene between the design of a system and the production process that creates conditions in which errors are more likely to happen. James Reason refers to these factors as psychological precursors or preconditions.[40] Although good managerial decisions are required for safe and efficient production, they are not sufficient. There is also a need to have the right equipment, well-maintained and reliable; a skilled and knowledgeable workforce; reasonable work schedules, well-designed jobs; clear guidance on desired and undesired performance, et cetera. Factors such as these are the precursors or preconditions for safe production processes.

Any given precondition can contribute to a large number of unsafe acts. For example, training deficiencies can show up as high workload, undue time pressure, inappropriate perception of hazards, or motivational difficulties.[41] Preconditions are latent failures embedded in the system. Designing safe systems means taking into account people's psychological limits and either seeking ways to eliminate the preconditions or intervening to minimize their consequences. Job design, equipment selection and use, operational procedures, work schedules, and so forth, are all factors in the production process that can be designed for safety.

One specific type of precondition that receives a lot of attention is technology. The occurrence of human error creates the perception that humans are unreliable and inefficient. One response to this has been to find the unreliable person who committed the error and focus on preventing him or her from doing it again. Another response has been to increase the use of technology to automate processes so as to remove opportunities for humans to make errors. The growth of technology over the past several decades has contributed to system complexity so this particular issue is highlighted here.

Technology changes the tasks that people do by shifting the workload and eliminating human decision making.[42] Where a worker previously may have overseen an entire production process, he or she may intervene now only in the last few steps if the previous steps are automated. For example, flying an aircraft has become more automated, which has helped reduce workload during nonpeak periods. During peak times, such as take-off and landing, there may be more processes to monitor and information to interpret.

Furthermore, the operator must still do things that cannot be automated. This usually involves having to monitor automated systems for rare, abnormal events[43] because machines cannot deal with infrequent events in a constantly changing environment.[44] Fortunately, automated systems rarely fail. Unfortunately, this means that

operators do not practice basic skills, so workers lose skills in exactly the activities they need in order to take over when something goes wrong.

Automation makes systems more "opaque" to people who manage, maintain, and operate them.[45] Processes that are automated are less visible because machines intervene between the person and the task. For example, automation means that people have less hands-on contact with processes and are elevated to more supervisory and planning tasks. Direct information is filtered through a machine (e.g., a computer), and operators run the risk of having too much information to interpret or of not getting the right information.

In the case study, the infusion device administered the medication and the professional monitored the process, intervening when problems arose. The medication administration process was "opaque" in that the device provided no feedback to the user when the medication flowed freely and minimal feedback when the medication flow was blocked.

One of the advantages of technology is that it can enhance human performance to the extent that the human plus technology is more powerful than either is alone.[46] Good machines can question the actions of operators, offer advice, and examine a range of alternative possibilities that humans cannot possibly remember. In medicine, automated order entry systems or decision support systems have this aim. However, technology can also create new demands on operators. For example, a new piece of equipment may provide more precise measurements, but also demand better precision from the operator for the equipment to work properly.[47] Devices that have not been standardized, or that work and look differently, increase the likelihood of operator errors. Equipment may not be designed using human factors principles to account for the human–machine interface.[48]

In the case study, safer systems could have been designed by taking into consideration characteristics of how people use machines and interact with each other in teams. For example:

- *Redesign the devices to default to a safe mode*
- *Reduce the difficulties of using multiple devices simultaneously*
- *Minimize the variety of equipment models purchased*
- *Implement clear procedures for checking equipment, supplies, etc., prior to beginning surgery*
- *Orient and train new staff with the team(s) with which they will work*
- *Provide a supportive environment for identifying and communicating about errors for organizational learning and change to prevent errors.*

Technology also has to be recognized as a "member" of the work team. When technology shifts workloads, it also shifts the interactions between team members.

Where processes may have been monitored by several people, technology can permit the task to be accomplished by fewer people. This affects the distributed nature of the job in which tasks are shared among several people and may influence the ability to discover and recover from errors.[49]

In this context, technology does not involve just computers and information technology. It includes "techniques, drugs, equipment and procedures used by health care professionals in delivering medical care to individuals and the systems within which such care is delivered."[50] Additionally, the use of the term technology is not restricted to the technology employed by health care professionals. It can also include people at home of differentages, visual abilities, languages, and so forth, who must use different kinds of medical equipment and devices. As more care shifts to ambulatory and home settings, the use of medical technology by non-health professionals can be expected to take on increasing importance.

RESEARCH ON HUMAN FACTORS

Research in the area of human factors is just beginning to be applied to health care. It borrows from the disciplines of industrial engineering and psychology. *Human factors is defined as the study of the interrelationships between humans, the tools they use, and the environment in which they live and work.*[51]

In the context of this report, a human factors approach is used to under- stand where and why systems or processes break down. This approach examines the process of error, looking at the causes, circumstances, conditions, associated procedures and devices and other factors connected with the event. Studying human performance can result in the creation of safer systems and the reduction of conditions that lead to errors. However, not all errors are related to human factors. Although equipment and materials should take into account the design of the way people use them, human factors may not resolve instances of equipment breakdown or material failure.

Much of the work in human factors is on improving the human–system interface by designing better systems and processes.[52] This might include, for example, simplifying and standardizing procedures, building in redundancy to provide backup and opportunities for recovery, improving communications and coordination within teams, or redesigning equipment to improve the human–machine interface.

Two approaches have typically been used in human factors analysis. The first is critical incident analysis. Critical incident analysis examines a significant or pivotal occurrence to understand where the system broke down, why the incident occurred, and the circumstances surrounding the incident.[53] Analyzing critical incidents, whether or not the event actually leads to a bad outcome, provides an

understanding of the conditions that produced an actual error or the risk of error and contributing factors.

In the case study, researchers with expertise in human factors could have helped the team investigate the problem. They could examine how the device performed under different circumstances (e.g., what the alarms and displays did when the medication flow changed), varying the setup and operation of the infusion device to observe how it performed under normal and abnormal conditions. They could observe how the staff used the particular infusion device during surgery and how they interacted with the use of multiple infusion devices.

A critical incident analysis in anesthesia found that human error was involved in 82 percent of preventable incidents. The study identified the most frequent categories of error and the riskiest steps in the process of administering anesthesia. Recommended corrective actions included such things as labeling and packaging strategies to highlight differences among anesthesiologists in the way they prepared their workspace, training issues for residents, work–rest cycles, how relief and replacement processes could be improved, and equipment improvements (e.g., standardizing equipment in terms of the shape of knobs and the direction in which they turn).

Another analytic approach is referred to as "naturalistic decision making."[54] This approach examines the way people make decisions in their natural work settings. It considers all of the factors that are typically controlled for in a laboratory-type evaluation, such as time pressure, noise and other distractions, insufficient information, and competing goals. In this method, the researcher goes out with workers in various fields, such as firefighters or nurses, observes them in practice, and then walks them through to reconstruct various incidents. The analysis uncovers the factors weighed and the processes used in making decisions when faced with ambiguous information under time pressure.

In terms of applying human factors research, David Woods of Ohio State University describes a process of reporting, investigation, innovation, and dissemination (David Woods, personal communication, December 17, 1998). Reporting or other means of identifying errors tells people where errors are occurring and where improvements can be made. The investigation stage uses human factors and other analyses to determine the contributing factors and circumstances that created the conditions in which errors could occur. The design of safer systems provides opportunities for innovation and working with early adopters to test out new approaches. Finally, dissemination of innovation throughout the industry shifts the baseline for performance. The experience of the early adopters redefines what is possible and provides models for implementation. Aviation has long analyzed the role of human factors in performance. The Ames Research Center (part of the National Aeronautics and Space Administration) has examined areas related to information technology, automation,

and the use of simulators for training in basic and crisis skills, for example. Other recent projects include detecting and correcting errors in flight; interruptions, distractions and lapses of attention in the cockpit; and designing information displays to assist pilots in maintaining awareness of their situation during flight.[55]

SUMMARY

The following key points can be summarized from this chapter.

1. Some systems are more prone to accidents than others because of the way the components are tied together. Health care services is a complex and technological industry prone to accidents.
2. Much can be done to make systems more reliable and safe. When large systems fail, it is due to multiple faults that occur together.
3. One of the greatest contributors to accidents in any industry including health care, is human error. However, saying that an accident is due to human error is not the same as assigning blame because most human errors are induced by system failures. Humans commit errors for a variety of known and complicated reasons.
4. Latent errors or system failures pose the greatest threat to safety in a complex system because they lead to operator errors. They are failures built into the system and present long before the active error. Latent errors are difficult for the people working in the system to see since they may be hidden in computers or layers of management and people become accustomed to working around the problem.
5. Current responses to errors tend to focus on the active errors. Although this may sometimes be appropriate, in many cases it is not an effective way to make systems safer. If latent failures remain unaddressed, their accumulation actually makes the system more prone to future failure. Discovering and fixing latent failures and decreasing their duration are likely to have a greater effect on building safer systems than efforts to minimize active errors at the point at which they occur.
6. The application of human factors in other industries has successfully reduced errors. Health care has to look at medical error not as a special case of medicine, but as a special case of error, and to apply the theory and approaches already used in other fields to reduce errors and improve reliability.[56]

32. Cook and Woods, 1994.
33. Reason. 1990.
34. Norman, 1993.
35. Perrow, 1984.
36. Perrow, 1984.
37. Cook, Woods and Miller, 1998.
38. On the other hand, in some places, the health system may be complex, but loosely coupled. For example, during an emergency, a patient may receive services from a loosely networked set of subsystems—from the ambulance to the emergency room to the outpatient clinic to home care. See Van Cott in Bogner, 1994.
39. Cook and Woods, 1994.
40. Reason, 1990.
41. Reason, 1990.
42. Cook and Woods, 1994.
43. Reason, 1990.
44. Van Cott, 1994.
45. Reason, 1990.
46. Norman, 1993.
47. Cook and Woods, 1994.
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49. Norman, 1993.
50. Institute of Medicine, *Assessing Medical Technologies*, Washington, D.C.: National Academy Press, 1985.
51. Weinger, Matthew B; Pantiskas, Carl; Wiklund, Michael; Carstensen, Peter. Incorporating Human Factors Into the Design of Medical Devices. *JAMA*. 280(17):1484, 1998.
52. Reason, 1990. Leape, 1994.
53. Cooper, Newbower, Long, et al., 1978.
54. Klein, Gary, *Sources of Power: How People Make Decisions*, Cambridge, MA: The MIT Press, 1998.
55. "Current Projects," Human Factors Research and Technology Division, Ames Research Center, NASA, http://human-factors.arc.nasa.gov/frameset.html
56. Senders, 1994.

APPENDIX 2
CHECKLIST FOR DEVELOPING A REPORTING SYSTEM

1. Clarify objectives

- Learning
- Accountability
- Both

2. What types of learning are the priorities?

- Alerts regarding significant new hazards
- Lessons learned by hospitals
- Analysis of trends
- Analysis of systems failures
- Recommendations for best practices

3. Voluntary or mandatory?

- Voluntary
- Mandatory

4. Confidential or public disclosure?

- Confidential
- Public disclosure of individual reports
- Public disclosure of analysis or trends

5. What is the process for the reporting system?

- What is reported?
- Who can report?
- How does one report?

6. Is confidential information held secure?

- Patient confidentiality
- Reporter confidentiality
- Organization confidentiality

7. What is the data infrastructure?

- Human receiver recognizing hazard reports
- Simple spreadsheet
- Relational database

8. What is the approach to classification?

- By event type
- By risk
- By causation

9. What is the approach to analysis?

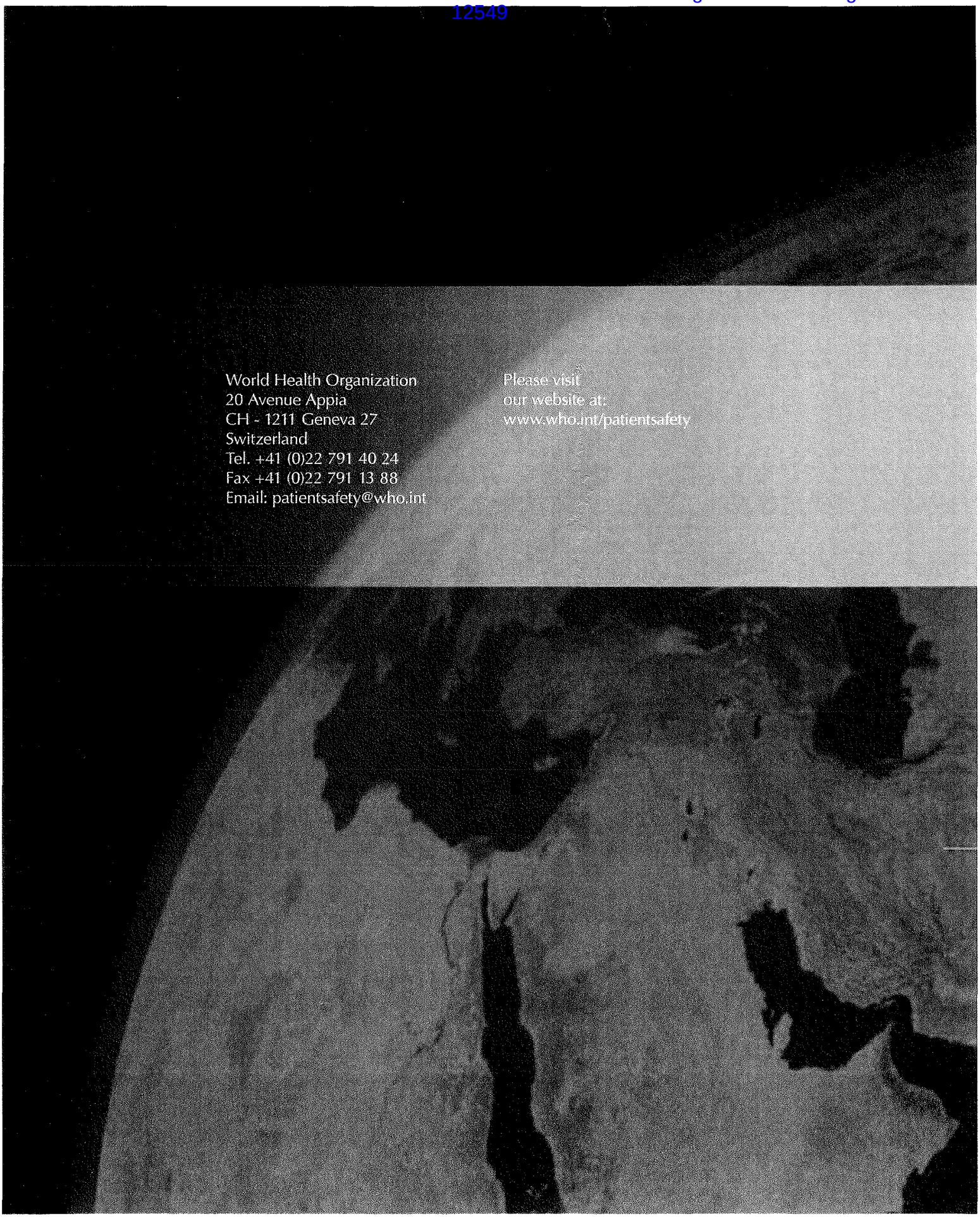
- Hazard identification
- Summaries and descriptions
- Trend and cluster analysis
- Correlations
- Risk analysis
- Causal analysis
- Systems analysis

10. How will responses be generated and disseminated?

- Acknowledgement to reporter
- Alerts generated to organizations
- Trends, themes, or best practices in periodic newsletters

11. Are there sufficient resources?

- Mechanism for collecting reports
- Database management
- Capacity to investigate
- Technical infrastructure
- Method for classifying events
- Expert analysis
- Capacity to disseminate findings and recommendations



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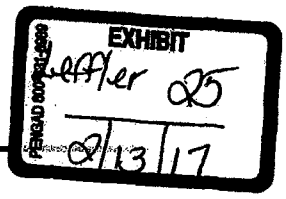

Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Industry[1] Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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I. INTRODUCTION

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).[2] Specifically, this document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

[1] This guidance has been prepared by the PDUFA III Pharmacovigilance Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For ease of reference, this guidance uses the term *product* or *drug* to refer to all products (excluding blood and blood components) regulated by CDER and CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

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A. PDUFA III's Risk Management Guidance Goal

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9 – 11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

B. Overview of the Risk Management Guidances

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

  Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (see e.g., FDA requirements for professional labeling, and adverse

event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

  During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.[3]

- To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as appropriate.

  The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

- When planning risk assessment and risk minimization activities, sponsors should consider input from health care participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and third party payers).

- There are points of overlap among the three guidances.

  We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

III. THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

[3] See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii), and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see http://www.hhs.gov/ocr/hipaa.

This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

A. Good Reporting Practice

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events,[4] and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

[4] Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on *Postmarketing Reporting of Adverse Experiences*, (3) FDA guidance for industry on *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)*, (4) FDA guidance for industry on *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

B. Characteristics of a Good Case Report

Good case reports include the following elements:

1. Description of the adverse events or disease experience, including time to onset of signs or symptoms;

2. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;

3. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;

4. Documentation of the diagnosis of the events, including methods used to make the diagnosis;

5. Clinical course of the event and patient outcomes (e.g., hospitalization or death);[5]

6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;

7. Information about response to dechallenge and rechallenge; and

8. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following, when such information is available:

1. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);

2. Sequence of events leading up to the error;

3. Work environment in which the error occurred; and

4. Types of personnel involved with the error, type(s) of error, and contributing factors.

[5] Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy.[6] Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

C. Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)). When available, FDA recommends that standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.[7] In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);

2. Absence of symptoms related to the event prior to exposure;

3. Evidence of positive dechallenge or positive rechallenge;

4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;

5. Consistency of the event with the known effects of other products in the class;

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[6] See http://www.nccmerp.org for the definition of a medication error and taxonomy of medication errors.

[7] See, for example, Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and

7. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories *probable, possible,* or *unlikely* have been used previously.[8] If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event.[9] FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the *medication use systems* (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors.

D. Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. The clinical and laboratory manifestations and course of the event;

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[8] See World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Product,* for additional categorizations of causality.

[9] See Cohen MR (ed), 1999, *Medication Errors*, American Pharmaceutical Association, Washington DC; Cousins DD (ed), 1998, *Medication Use: A Systems Approach to Reducing Errors*, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

2. Demographic characteristics of patients with events (e.g., age, gender, race);
3. Exposure duration;
4. Time from initiation of product exposure to the adverse event;
5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
6. Use of concomitant medications;
7. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
8. The route of administration (e.g., oral vs. parenteral);
9. Lot numbers, if available, for products used in patients with events; and
10. Changes in event reporting rate over calendar time or product life cycle.

E. Use of Data Mining to Identify Product-Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called *data mining*, can provide additional information about the existence of an excess of adverse events reported for a product. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with (2) the fraction of reports for the same particular event for all drugs (i.e.,"the expected reporting fraction").[10] This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product-event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product-event combination with a score exceeding the specified threshold. When

[10] Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

applying data mining to large databases (such as AERS), it is not unusual for a product to have several product-event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm[11,12], the Proportional Reporting Ratio (PRR) method[13,14]and the Neural Network approach.[15] Except when the observed number of cases with the drug event combination is small (e.g., less than 20) or the expected number of cases with the drug event combination is < 1, the MGPS and PRR methods will generally identify similar drug event combinations for further investigation.[16]

Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products. FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g., some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other co-morbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, under-reporting, or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g., statistical algorithm, and the drugs, events and

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[11] DuMouchel W and Pregibon D, 2001, Empirical Bayes screening for multi-item associations, *Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining.*

[12] Szarfman A, Machado SG, and O'Neill RT, 2002, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety* 25(6): 381-92.

[13] Evans SJW, Waller P, and Davis S, 1998, Proportional reporting ratios: the uses of epidemiological methods for signal generation [abstract], *Pharmacoepidemiology and Drug Safety* 7:S102.

[14] Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

[15] Bate A et al., 1998, A Bayesian neural network method for adverse drug reaction signal generation, *European Journal of Clinical Pharmacology* 54:315-21.

[16] This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, M.D., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

stratifications selected for the analyses) or an appropriate reference, and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug-event combination of interest (e.g., results from preclinical, clinical, pharmacoepidemiologic, or other available studies).

F. Safety Signals That May Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. New unlabeled adverse events, especially if serious;
2. An apparent increase in the severity of a labeled event;
3. Occurrence of serious events thought to be extremely rare in the general population;
4. New product-product, product-device, product-food, or product-dietary supplement interactions;
5. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);
6. Confusion about a product's name, labeling, packaging, or use;
7. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);
8. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal);[17] and
9. Other concerns identified by the sponsor or FDA.

G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment.

[17] For a detailed discussion of risk minimization action plan evaluation, please consult the *RiskMAP Guidance*.

In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because:

1. Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;

2. It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low;[18] and

3. A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator.[19,20] FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from: (1) national health statistics, (2) published medical literature, or (3) ad hoc studies, particularly of

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[18] See *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

[19] See Rodriguez EM, Staffa JA, Graham DJ, 2001, *The role of databases in drug postmarketing surveillance*, Pharmacoepidemiology and Drug Safety, 10:407-10.

[20] In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria, and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the "real world" and randomized trials. The *Premarketing Guidance* discusses a number of types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

A. Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover, or other models.[21] The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse

[21] *Guidelines for Good Pharmacoepidemiology*, , International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/resources/guidelines_08027.cfm)

event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing (e.g., to study the natural history of disease or patterns of product use, or to estimate background rates for adverse events).

For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10,000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event–product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study.[22] Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

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[22] See, for example, Strom BL (ed), 2000, *Pharmacoepidemiology*, 3rd edition, Chichester: John Wiley and Sons, Ltd; Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology: An Introduction*, 3rd edition, Cincinnati, OH: Harvey Whitney Books.

There are a number of references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations,[23] and providing guidelines to facilitate the conduct, interpretation, and documentation of such studies.[24] Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes:

1. Clearly specified study objectives;
2. A critical review of the literature; and
3. A detailed description of the research methods, including:
   - the population to be studied;
   - the case definitions to be used;
   - the data sources to be used (including a rationale for data sources if from outside the U.S.);
   - the projected study size and statistical power calculations; and
   - the methods for data collection, management, and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. Demographic characteristics of patients enrolled in the health plans (e.g., age, geographic location);

2. Turnover rate of patients in the health plans;

3. Plan coverage of the medications of interest;

4. Size and characteristics of the exposed population available for study;

5. Availability of the outcomes of interest;

6. Ability to identify conditions of interest using standard medical coding systems (e.g., International Classification of Diseases (ICD-9)), procedure codes or prescriptions that could be used as markers;

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[23] Ibid.

[24] *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/resources/guidelines_08027.cfm).

7. Access to medical records; and

8. Access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

B. Registries

The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects."[25] Whenever possible, a control or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest).[26]

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.[27] Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases; and

2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved, or when there is a need to evaluate

[25] See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at http://www.ncvhs.hhs.gov.

[26] See for example, FDA Guidance for Industry, *Establishing Pregnancy Exposure Registries*, August 2002 http://www.fda.gov/cder/guidance/3626fnl.pdf.

[27] Ibid.

safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. The types of additional risk information desired;
2. The attainability of that information through other methods; and
3. The feasibility of establishing the registry.

Sponsors electing to initiate a registry should develop written protocols that provide: (1) objectives for the registry, (2) a review of the literature, and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of: (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management, and analysis, and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and we encourage sponsors to discuss their registry development plans with FDA.

C. Surveys

Patient or health care provider surveys can gather information to assess, for example:

1. A safety signal;

2. Knowledge about labeled adverse events;

3. Use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist;

4. Compliance with the elements of a RiskMAP (e.g., whether or not a Medication Guide was provided at the time of product dispensing); and [28]

5. Confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including: (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management, and analysis.[29] FDA recommends that a survey-based monitoring

[28] For a detailed discussion of RiskMAP evaluation, please consult the *RiskMAP Guidance*.

[29] See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

system include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g., from preclinical or other sources), FDA suggests that a sponsor consider further study (e.g., observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from preclinical findings to current observations. This submission should include the following:

1. Spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;

2. Background rate for the event in general and specific patient populations, if available;

3. Relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies;

4. Biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;

5. Safety findings from controlled clinical trials; and

6. General marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provide an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations, and, if appropriate, (1) propose steps to further investigate the signal through additional studies, and (2) propose risk

minimization actions.[30] FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class) and will communicate its conclusions to the sponsor whenever possible. Factors that are typically considered include:

1. Strength of the association (e.g., relative risk of the adverse event associated with the product);
2. Temporal relationship of product use and the event;
3. Consistency of findings across available data sources;
4. Evidence of a dose-response for the effect;
5. Biologic plausibility;
6. Seriousness of the event relative to the disease being treated;
7. Potential to mitigate the risk in the population;
8. Feasibility of further study using observational or controlled clinical study designs; and
9. Degree of benefit the product provides, including availability of other therapies.

As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps.[31] FDA recommends that assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket requirements under the FDCA and FDA implementing regulations) is sufficient for postmarketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A

[30] In the vast majority of cases, risk communication that incorporates appropriate language into the product's labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the *RiskMAP Guidance* for a complete discussion of RiskMAP development.

[31] For additional discussion of the relationship between risk assessment and risk minimization, please consult the *RiskMAP Guidance*.

pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.[32] The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;

2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);

3. The severity of the event;

4. The nature of the population(s) at risk;

5. The range of patients for which the product is indicated (broad range or selected populations only); and

6. The method by which the product is dispensed (through pharmacies or performance linked systems only).[33]

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP), as described in the *RiskMAP Guidance*. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.

FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for postmarketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious safety risks have been identified pre- or post-approval, or (2) at-risk populations have not been adequately studied.

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[32] As used in this document, the term "pharmacovigilance plan" is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a "pharmacovigilance plan" would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

[33] For a detailed discussion of controlled access systems, please consult the *RiskMAP Guidance*.

Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports);

2. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);

3. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure);

4. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs (see section V);

5. Creation of registries or implementation of patient or health care provider surveys (see section V); and

6. Additional controlled clinical trials.[34]

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks: (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question, or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. While additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g., through labeling) to minimize the risk to users of the product.

[34] For a discussion of risk assessment in controlled clinical trials, please consult the *Premarketing Guidance*.

Exhibit Z

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW JERSEY

- - -

IN RE: BENICAR (Olmesartan) PRODUCT LIABILITY LITIGATION	:	CIVIL ACTION
	:	NO. 15-2606 (RBK)(JS)

- - -

February 28, 2017

- - -

PROTECTED INFORMATION

Oral deposition of SUSAN HUFTLESS, Ph.D., taken pursuant to notice, was held at the law offices of Venable, LLP, 750 East Pratt Street, Suite 900, Baltimore, Maryland, beginning at 8:36 a.m., on the above date, before Michelle L. Gray, a Registered Professional Reporter, Certified Shorthand Reporter, Certified Realtime Reporter, and Notary Public.

- - -

GOLKOW TECHNOLOGIES, INC.
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

APPEARANCES: (Cont'd.)

ALSO PRESENT:

Amy Klug (Daiichi-Sankyo)
(Via telephone)

- - -

would be fixed as one, a yes, one point.

Number 3, "Did the adverse reaction improve when the drug was discontinue or specific antagonist was administered?" I'm sorry. That was about temporality. Number 3 is about dechallenge. That would also receive a score of one.

The next question, Number 4, is about rechallenge. "Did the adverse event reappear when the drug was readministered?" That would be given a score of two.

Question Number 5, "Are there alternative causes other than the drug that could on their own have caused a reaction?" This is one of the items that would be assessed using the three questions that I mentioned about comorbidities, medications, and allergies. That's an unknown at this point, no score yet.

Question Number 6, "Did the reaction reappear when placebo was

given?" This is when we're really getting to the point where I'm finding it hard to apply Naranjo because this just doesn't apply, because the manufacturer never included olmesartan-induced enteropathy or celiac disease or any of the other symptoms that are associated with olmesartan-induced enteropathy as defined endpoints in their files. So I can't assess this one. It's given as a zero point for that reason.

"Was the drug detected in blood or other fluids in concentrations known to be toxic?" Again, there was no drug detection. There's no test for this. That's a score of zero.

"Was the reaction more severe when the dose is increased or less severe when the dose was decreased?" Based on my conversations with Dan in clinical practice, you prescribe the patient a dose, and there isn't -- for some drugs, you'll actually up-titrate or down-titrate. That doesn't happen with

olmesartan-induced enteropathy. In this case that would be assumed to be assessed as zero for all.

The next one, "Did the patient have a similar reaction to the same or similar drugs in any previous exposure?" And this is one of them that we struggled with in the wording, because we felt this would be exactly the same as rechallenge. You'll see that conversation that you were asking me about, about Naranjo 9, is exactly the same conversation. It's a frustrating question.

We assume this would be the same as rechallenge and assigned this a one.

Number 10, "Was the adverse event confirmed by any objective evidence?" This would need to be assessed on a case-by-case basis. So if you add those up. You get -- one, two, three, four, five six -- you end up with six actually even before going to the

AA

Exhibit AA

2009 WL 2058384
United States District Court,
S.D. Florida.

Douglas C. KILPATRICK, Plaintiff,
v.
BREG, INC., Defendant.

No. 08–10052–CIV.
|
June 25, 2009.

West KeySummary

1 Evidence
Medical testimony

Evidence
References to authorities on subject

Medical device manufacturer's motion to exclude expert physician's causation testimony and expert opinion on the causation of chondrolysis was granted in patient's product liability claims against medical device manufacturer. Patient proffered an extensive list of articles that expert physician purportedly relied upon in preparing his expert report; however, expert physician pointed to only four articles that supported his conclusion that bupivacaine delivered via an intra-articular pain pump catheter could cause chondrolysis. Only one of the articles was a comparative study of humans who had undergone arthroscopic surgery involving pain pumps. None of the articles explained the mechanism by which bupivacaine damages cartilage, and none of the articles offered an ultimate conclusion as to the general causation of glenohumeral chondrolysis. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

23 Cases that cite this headnote

Attorneys and Law Firms

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ORDER GRANTING DEFENDANT'S MOTION FOR SUMMARY JUDGMENT; GRANTING DEFENDANT'S MOTION TO EXCLUDE CAUSATION TESTIMONY

K. MICHAEL MOORE, District Judge.

***1** THIS CAUSE came before the Court upon Breg's Motion for Summary Judgment (dkt # 69) and Breg's Motion to Exclude Causation Testimony (dkt # 71).

UPON CONSIDERATION of the Motions, the responses, the pertinent portions of the record, and being otherwise fully advised in the premises, the Court enters the following Order.

I. BACKGROUND

Plaintiff Douglas Kilpatrick ("Kilpatrick") is the owner and operator of a charter fishing guide service in the Florida Keys. In 2004, Kilpatrick visited orthopedic surgeon Dr. John Papilion ("Papilion"), complaining of pain in his right shoulder. Papilion performed an X-ray and an MRI scan which identified a tear in Kilpatrick's labrum, the ring of tissue that surrounds the shoulder socket, or glenoid. To correct the problem, Papilion performed arthroscopic shoulder surgery on Kilpatrick on October 5, 2004.

In order to control post-operative pain, Papilion, during the surgery, inserted into Kilpatrick's shoulder joint a pain pump manufactured by Defendant, Breg, Inc. ("Breg"). Kilpatrick alleges that per Breg's product instructions, Papilion then injected 20 cc's of the anesthetic .5% bupivacaine [1] via the pain pump's attached catheter into Kilpatrick's shoulder, and further filled the pump with

100 cc's of bupivacaine, which the pump was to deliver into Kilpatrick's shoulder over the next forty-eight hours. Kilpatrick successfully completed post-operative physical therapy and was able to return to work for the 2005 fishing season. Kilpatrick claims that while working during that season, he noticed some popping in his shoulder, but at the end of the season felt better.

1 A trade name for bupivacaine is "marcaine," and the Parties' filings use both names. Kilpatrick's causation expert has testified that both names refer to the same chemical. *See* Deposition of Dr. Gary Poehling, at pp. 63:8–9 (dkt # 72–2) (hereinafter "Poehling Dep."). For convenience, this Order will use the term "bupivacaine." It is undisputed that Breg manufactured only the pain pump used in Kilpatrick's surgery, not the bupivacaine.

However, during the 2006 season, Kilpatrick claims he began to experience severe shoulder pain and limited motion while working. Kilpatrick returned to Papilion, who, after additional testing, diagnosed Kilpatrick in October of 2006 with glenohumeral chondrolysis—a breakdown of the cartilage in Kilpatrick's shoulder joint. On November 13, 2006, orthopedic surgeon Dr. John Uribe ("Uribe") performed a total shoulder replacement on Kilpatrick. Kilpatrick states that he will have to undergo several more such procedures during his lifetime.

On July 28, 2008, Kilpatrick filed the instant Complaint (dkt # 1). Kilpatrick alleges that, as a direct result of being administered bupivacaine via Breg's pain pump, he now suffers from permanent and incurable injuries, including debilitating shoulder pain, that have severely and negatively impacted his ability to work, resulting in economic harm in the form of past and future medical expenses. The Complaint asserts five strict product liability claims against Breg for design defect (Count I), defect due to inadequate warning (Count II), defect due to nonconformance with representations (Count III), and defect due to failure to adequately test (Count IV). The Complaint also includes a claim for negligence (Count V), and for violation of the Florida Deceptive and Unfair Trade Practices Act, §§ 501.201–213, Florida Statutes (Count VI).

***2** Breg has filed a motion pursuant to Federal Rule of Evidence 702 to exclude Kilpatrick's evidence of the causation of his injury (dkt # 71). Breg has also moved for summary judgment (dkt # 69) on the grounds that Kilpatrick has not sufficiently demonstrated that Breg's pain pump could and did cause the type of injury Kilpatrick suffered.

II. DISCUSSION

Because the resolution of Breg's summary judgment motion turns on whether Kilpatrick has provided enough admissible evidence to show an issue of material fact as to whether Breg's pain pump caused Kilpatrick's injury, the Court finds it appropriate to first resolve Breg's Rule 702 motion. [2]

2 As a threshold matter, the Court notes that it has jurisdiction over this matter pursuant to 28 USC § 1332 because the Parties are diverse and the amount in controversy exceeds $75,000. The Parties stipulate that Florida substantive law on strict products liability and negligence applies. *See* Amended Pretrial Stipulation at p. 4 (dkt # 155).

A. *Breg's Motion to Exclude Causation Testimony*

1. *Standard of Review*

Federal Rule of Evidence 702 sets out the following requirements for expert testimony:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed.R.Evid. 702. The U.S. Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), and its progeny, govern the application of Rule 702.

Under Rule 702 and *Daubert,* district courts must act as "gatekeepers," admitting expert testimony only if it is both

reliable and relevant, to prevent speculative and unreliable testimony from reaching the jury. *Rink v. Cheminova, Inc.,* 400 F.3d 1286, 1291 (11th Cir.2005). Specifically, the district court must consider whether 1) the expert is qualified to testify competently regarding the matters he intends to address; 2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert;* and 3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue. *City of Tuscaloosa v. Harcros Chems., Inc.,* 158 F.3d 548, 562–63 (11th Cir.1998) (footnote omitted). In the Eleventh Circuit, these three considerations are known as "qualifications, reliability, and helpfulness," and must not be conflated by the district court. *U.S. v. Frazier,* 387 F.3d at 1246, 1260 (11th Cir.2004). The party offering the expert bears the burden of satisfying each of the three elements by a preponderance of the evidence. *Rink,* 400 F.3d at 1292 (citations omitted).

The district court enjoys "broad latitude" in deciding whether expert testimony is reliable, and in how to conduct that inquiry. *See Toole v. Baxter Healthcare Corp.,* 235 F.3d 1307, 1312 (11th Cir.2000) (citing *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 142, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999)). "This deferential standard is not relaxed even though a ruling on the admissibility of expert evidence may be outcome-determinative." *Allison v. McGhan Medical Corp.,* 184 F.3d 1300, 1306 (11th Cir.1999) (citing *General Electric Co. v. Joiner,* 522 U.S. 136, 142–43, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)).

***3** With the foregoing in mind, the Court has reviewed the voluminous record in this case, including the expert report of Dr. Gary Poehling, M.D. ("Poehling"), Poehling's deposition testimony, and the medical literature upon which he based his opinions, and has concluded that his testimony on the causation of chondrolysis must be excluded pursuant to Rule 702. [3]

3 Because Poehling's testimony must be excluded for failure to satisfy Rule 702's reliability prong, the Court does not reach the helpfulness prong.

2. *Qualifications*

Poehling easily meets the qualification prong of Rule 702. The qualification standard for expert testimony is "not stringent," and "so long as the expert is minimally qualified, objections to the level of the expert's expertise [go] to credibility and weight, not admissibility." *Hendrix v. Evenflo Co., Inc.,* 255 F.R.D. 568, 585 (N.D.Fla.2009) (citations and quotation marks omitted). Breg does not challenge Poehling's qualifications to opine on the cause of chondrolysis, conceding that Poehling has had a long and accomplished career in the field of orthopedics, has been an editor on one of the nation's leading peer-reviewed orthopedics journals for twenty years—serving as editor-in-chief since 1992—has been a practicing orthopedic surgeon and professor of orthopedics, and has authored numerous lectures, speeches, articles, and other writings on topics related to orthopedics. *See* Poehling Curriculum Vitae (dkt # 104–7). The Court finds that Poehling is more than minimally qualified to offer an opinion on the cause of Kilpatrick's injury.

3. *Reliability*

The reliability prong of Rule 702 is at the heart of the Parties' dispute. The reliability inquiry requires the court to independently analyze each step in the logic leading to the expert's conclusions; if the court determines that any step in the expert's chain of logic is unreliable, his entire opinion must be excluded. *McClain v. Metabolife Int'l Inc.,* 401 F.2d 1233, 1245 (11th Cir.2005). In determining reliability, the Court may consider the following non-exclusive factors: "(1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4) whether the technique is generally accepted in the scientific community." *See McCorvey v. Baxter Healthcare Corp.,* 298 F.3d 1253, 1256 (11th Cir.2002) (citing *Daubert,* 509 U.S. at 593–94).

However, these factors are not the "definitive checklist or test" for reliability, *see Daubert,* 509 U.S. at 593, and in some cases, evidence which does not meet all or even most of these factors may still be admissible, because other factors may predominate. *U.S. v. Brown,* 415 F.3d 1257, 1267–68 (11th Cir.2005). Although the pertinent criteria for reliability may vary case by case, to be reliable the expert's testimony must always be based on "good grounds," *see Daubert,* 509 U.S. at 590; "leaps of faith" unsupported by good science preclude the admission of the expert's testimony. *Rider v. Sandoz Pharmaceuticals,* 295 F.3d 1194, 1202 (11th Cir.2002). The objective of the gatekeeping inquiry "is to make certain that an expert, whether basing testimony upon professional studies or

personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co.,* 526 U.S. at 152.

***4** Breg argues, and Kilpatrick does not contest, that this case should be treated like a toxic tort case for purposes of the *Daubert* inquiry, requiring Kilpatrick to offer proof of both general causation—whether the agent in question can cause harm of the type Kilpatrick alleges—and proof of specific causation—whether the agent in fact did cause Kilpatrick's injury. *See McClain,* 401 F.3d at 1239. If anything, determining causation in this case requires an even more complex logical chain than the typical toxic tort case, because the key issue is not merely whether a chemical compound could and did cause injury, but whether that compound as delivered via a particular medical device inserted in a particular location (within Kilpatrick's shoulder joint) could and did cause injury. Poehling has acknowledged this distinction, stating that he does not believe it is Breg's pain pump *per se* that causes chondrolysis, but the bupivacaine delivered via the pain pump that causes it. *See* Poehling Dep., at pp. 99:2–6 (dkt # 72–2) ("I don't think an intra-articular catheter causes glenohumeral chondrolysis. I think it is the bupivacaine that goes through that catheter that causes the glenohumeral chondrolysis."). Further, the Parties do not dispute that glenohumeral chondrolysis is a medical phenomenon that has emerged only recently, and that the first study suggesting its linkage with intra-articular pain catheters appeared only in 2006. Even Kilpatrick concedes that the medical literature supporting his claim is still a "developing science." *See* Pl.'s Resp. to Def. Mot. for Summ. J., at p. 6 (dkt # 102). It is almost *de rigeur* in *Daubert* opinions to quote Judge Posner's observation that "[l]aw lags science; it does not lead it," *Rosen v. Ciba–Geigy Corp.,* 78 F.3d 316, 319 (7th Cir.1996), but in light of the foregoing, it is particularly true in this case. Accordingly, the general causation inquiry takes on special importance here.

a. *Literature Poehling Relies on Is Insufficient to Show Causation*

In reaching his conclusions on general causation in this case, Poehling did not personally conduct any independent research; rather, he relied upon several medical journal articles. *See* Poehling Dep. at pp. 37:6–38:8 (dkt # 72–2). Poehling acknowledges that none of those articles were based on controlled, randomized epidemiological studies of human beings, which traditionally are considered the best form of statistical evidence for proving causation.[4] Kilpatrick argues, plausibly, that randomized human epidemiological studies would not be ethical or feasible under the circumstances and that such studies are not necessary to carry his burden on a *Daubert* motion. It is true enough that a lack of epidemiological evidence is not fatal to Kilpatrick's case. *See Rider,* 295 F.3d at 1199. But this only heightens the need for Poehling to present other forms of highly persuasive scientific evidence to lay a foundation for his expert opinions. He has failed to do so.

4 "Epidemiology, a field that concerns itself with finding the causal nexus between external factors and disease, is generally considered to be the best evidence of causation in toxic tort actions." *Rider,* 295 F.3d at 1198.

***5** Kilpatrick proffers an extensive list of articles that Poehling purportedly relied upon in preparing his expert report. However, when questioned during his deposition as to which articles support his conclusion that bupivacaine delivered via an intra-articular pain pump catheter can cause chondrolysis, Poehling pointed only to four[5]: a study of 152 patients who had undergone arthroscopic shoulder surgery (the "Hansen study"),[6] a study of rabbits whose shoulders were injected with bupivacaine (the "Gomoll study"),[7] a case report of two teenage female arthroscopic surgery patients who developed chondrolysis (the "Greis report"),[8] and a one-page editorial that Poehling had co-authored.[9] Only the first of these articles was a comparative study of humans who had undergone arthroscopic surgery involving pain pumps. Significantly, none of the articles explains the mechanism by which bupivacaine damages cartilage,[10] each has important limitations that Poehling does not take into account,[11] and none of them offers an ultimate conclusion as to the general causation of glenohumeral chondrolysis. At best, some of them tend to show an association between chondrolysis and intra-articular pain pump use, but as the Eleventh Circuit has recognized, "showing *association* is far removed from proving *causation.*" *Allison,* 184 F.3d at 1315 n. 16 (emphasis in original); *see also In re Accutane Prods. Liability Litig.,* 511 F.Supp.2d 1288, 1297 (M.D.Fla.2007) ("[A]n association is not equivalent to causation ...")

(citations omitted). The Court will now review each of these articles in turn.

5 *See* Poehling Dep., at pp. 43:20–45:10; 143:8–147:17 (dkt # 72–2).

6 Brent P. Hansen et al., *Postarthroscopic Glenohumeral Chondrolysis,* 35 Am. J. Sports Med., July 2007, 1628–34 (dkt # 72–3).

7 Andreas Gomoll et al., *Chondrolysis After Continuous Intra–Articular Bupivacaine Infusion: An Experimental Model Investigating Chondrotoxicity in the Rabbit Shoulder,* 22 Arthroscopy, Aug. 2006, 813–19. (dkt # 105–2).

8 Patrick Greis et al., *Bilateral Shoulder Chondrolysis Following Arthroscopy: A Report of Two Cases,* 90 J. Bone & Joint Surgery, June 2008, 1338–44 (dkt # 105–7).

9 James Lubowitz & Gary Poehling, *Editorial,* 25 Arthroscopy, July 2007, 223, 223 (dkt # 105–8).

10 *See In re Accutane Prods. Liability Litig.,* 511 F.Supp.2d 1288, 1295 (M.D.Fla.2007) (excluding expert testimony where "no one knows the biological mechanism by which [the condition in question] occurs").

11 *See id.* at 1291 ("When an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study. That is, he must not draw overreaching conclusions.") (*citing McClain,* 401 F.3d at 1245–47).

Poehling characterizes the Hansen study (dkt # 72–3) as the "strongest" evidence for a connection between intra-articular pain pumps and chondrolysis. *See* Poehling Dep., at p. 145:13–17 (dkt # 72–2). The Hansen study examined 152 patients who underwent 177 shoulder surgeries. Only nineteen shoulders in seventeen patients had bupivacaine-dispensing pain pumps inserted into them. Of those, twelve shoulders in ten patients developed chondrolysis. Kilpatrick, and Poehling, claim that this 63% injury rate (i.e. twelve chondrolytic shoulders out of nineteen treated with pain pumps) is powerful evidence of general causation. However, the Hansen study includes no statistical analysis, and therefore no means of determining whether the findings are statistically significant, or whether it is statistically meaningful to extrapolate from the relatively small sample size. Further, the study noted that thermal energy, another suspected cause of chondrolysis, was used in four cases, but did not explain whether thermal energy contributed to or wholly accounted for the chondrolysis in those cases, beyond a vague statement that "it [thermal energy] does not appear to be clearly proven to be the only factor in these cases." *See* Hansen study (dkt # 72–3, at 14). The study purported to identify a "strong association" between chondrolysis and intra-articular pain pumps, but also acknowledged that "[t]hermal and/or radiofrequency, suture material, and reabsorbable suture anchors may have played a role not yet completely understood at this time." *Id.* at 15. Unlike Poehling, the Hansen study declined to reach a conclusion as to the general causation of chondrolysis. Even assuming that arthroscopic shoulder surgery patients treated with intra-articular pain pumps suffer chondrolysis at the same rate observed in the Hansen study, nothing explains why nearly 40% of patients treated with pain pumps did not develop chondrolysis. In his deposition, Poehling acknowledged that he has no explanation:

> ***6** A.... You know, there is some reason that 40 percent of people that got in Hansen's study somehow survived—their articular cartilage survived, so is there something in those patients that are protective ... you have to say that there is a difference, because 40 percent didn't have it, so what is it that protected them. Is it something in the synovial fluid that is different, is there—is there some sort of protein that they have. You know, I don't know.

Poehling Dep., at pp. 138:23–139:10 (dkt # 72–2); *see also id.* at 103:14:–25. Extrapolating from the Hansen study that intra-articular pain pumps cause chondrolysis, then, effectively leaves an unexplained 40% error rate in Poehling's hypothesis. This is not the "good science" that *Daubert* and Rule 702 demand.

The second article on which Poehling based his conclusions, the Gomoll study, is a controlled study of rabbits (dkt # 105–2). The authors reported statistically significant evidence of chondrolysis among an experimental group of rabbits whose shoulders were infused with bupivacaine over a 48–hour period, as contrasted with a control group of rabbits injected with saline solution. However, the authors were careful to limit their conclusions, noting that further study was

warranted "because epidemiologic study of chondrolysis in humans will require an extremely large sample size because of the low incidence and prevalence of this condition ..." *Id.* at 6. The authors noted that "although we were able to show the detrimental effects of bupivacaine on the cellular and tissue level in a rabbit model, it remains to be determined whether human cartilage is equally susceptible and whether these ... changes result in the subsequent development of rapidly progressive osteoarthritis." *Id.* at 5. The courts have also recognized the difficulty inherent in extrapolating conclusions about human disease from animal-based studies. *See, e.g., Accutane,* 511 F.Supp.2d at 1291–1292 (discussing advantages and disadvantages of animal studies). One "significant disadvantage" of animal studies is that "differences in absorption, metabolism and other facts may result in interspecies variation in responses"; another disadvantage is that "the high doses customarily used in animal studies require consideration of the dose-response relationship and whether a threshold no-effect dose exists." *See id.* (quoting Michael D. Green et al., *Reference Guide on Epidemiology,* in *Reference Manual on Scientific Evidence,* 333, 345–46 (Federal Judicial Center, 2d. ed.2000)). This second consideration, the dose-response relationship, is particularly important here, because the authors of the Gomoll study acknowledge that "no data exist regarding the human-equivalent dosing of intra-articular bupivacaine in a rabbit shoulder model ..." *See* Gomoll study (dkt # 105–2 at 2). This admission undercuts the Gomoll study's applicability to human chondrolysis.

***7** The difference in the dose-response relationship between animals and humans is not trivial: dose-response relationship is, in fact, "the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect." *McClain,* 401 F.3d at 1242 (citing David Eaton, *Scientific Judgment and Toxic Torts: A Primer in Toxicology for Judges and Lawyers,* 12 J.L. & Pol'y 1, 11 (2003)).[12] "The expert who avoids or neglects this principle of toxic torts without justification casts suspicion on the reliability of his methodology." *Id.* In reaching his conclusions on human chondrolysis causation, Poehling did not account for or explain the possible differences in dose-response relationship between humans and rabbits, rendering his methodology questionable. *See Accutane,* 511 F.Supp.2d at 1292–93 (excluding expert testimony based in part on dog study where expert did not consider differences in dose-response relationship between dogs and humans).

12 Dose-response relationship is " '[a] relationship in which a change in amount, intensity, or duration of exposure to an agent is associated with a change—either an increase or decrease—in risk of disease.' " *McClain,* 401 F.3d at 1241–42 (citations omitted).

The third article upon which Poehling based his conclusion, the Greis report, was a report of two cases of female swimmers, one aged fourteen and the other eighteen, who developed chondrolysis after undergoing arthroscopic shoulder surgery involving bupivacaine-dispensing, intra-articular pain pumps (dkt # 105–7). Once again, the authors of the study were more cautious than Poehling in reaching an ultimate conclusion as to causation, acknowledging that "we realize that the exact cause of the chondrolysis remains unknown." *See id.* at 6. Furthermore, anecdotal reports of two individuals are, of course, not statistically significant evidence of causation. As Poehling acknowledges, case reports are "way down at the very bottom as far as medical strength of an article" and cannot establish medical causation. Poehling Dep., at p. 90:8–23 (dkt # 72–2). The Eleventh Circuit has likewise recognized that case reports on their own are not especially useful as proof of causation. *See McClain,* 401 F.3d at 1254 ("Simply stated, case reports raise questions; they do not answer them"); *Rider,* 295 F.3d at 1199 ("[W]hile they may support other proof of causation, case reports alone ordinarily cannot prove causation"). Accordingly, Poehling's extrapolation of a general cause for chondrolysis from this anecdotal case report is unwarranted and unreliable.

The final piece of literature Poehling claims to have relied upon is a 228–word editorial that Poehling himself co-authored (dkt # 105–8). The editorial is not a case report or study of any kind, and does not offer an opinion on the causation of chondrolysis, but rather states that "[t]he etiology of glenohumeral chondrolysis may be multifactorial. Further research is required to determine the cause, and proper prevention, of shoulder chondrolysis." *See id.* The editorial also notes that "idiopathic" chondrolysis—that is, chondrolysis caused by unknown factors—has also been described in the medical literature. *See id.* By Kilpatrick's own admission, the Poehling editorial "is general in nature and does not present any factual context that would allow the court to discern its relevance to this case." *See* Pl.'s Statement of

Material Facts in Opp. to Def.'s Mot. for Summ. J., at ¶ 3 (dkt # 103). The Poehling editorial is, to say the least, inadequate as a basis for a scientific judgment about the general causation of chondrolysis.

b. *Poehling Does Not Explain Background Risk*

***8** Even if the studies Poehling claims to have relied upon did support his conclusions about the causation of chondrolysis, there are additional problems with his methodology. Specifically, Poehling has not offered a sufficient explanation of the background risk for glenohumeral chondrolysis. Background risk "is not the risk posed by the chemical or drug at issue in the case. It is the risk a plaintiff and other members of the general public have of suffering the disease or injury that plaintiff alleges *without* exposure to the drug or chemical in question." *McClain,* 401 F.3d 1243 (emphasis in original). "A reliable methodology should take into account the background risk." *Id.*

Kilpatrick claims that the background risk of chondrolysis is "for all intent[s] and purposes zero." *See* Pl.'s Mem. in Opp. to Def.'s Mot. for Summ. J., at p. 1 (dkt # 102). But this is demonstrably incorrect. Poehling acknowledged in his editorial, and in his deposition, that chondrolysis can arise idiopathically—that is, from unknown causes. *See* Poehling Dep., at p. 70:10–20 (dkt # 72–2). If chondrolysis can occur without any known cause, it cannot be that the background risk for it is "zero." Whatever the true background risk, Poehling has not endeavored to explain it, and this casts further doubt on the reliability of his methodology.

c. *Poehling Concedes That the Literature Has Not Reached a Conclusion as to the Cause of Chondrolysis*

Although Kilpatrick offers Poehling's testimony for the purposes of proving general causation, Poehling, when asked in his deposition whether intra-articular pain pumps are still only a "hypothetical or speculative" cause of glenohumeral chondrolysis, repeatedly answered in the affirmative. Several exchanges from the transcript of his deposition are worth highlighting:

> Q: Do you agree, Dr. Poehling, that based on the available body of medical and scientific literature even today as of May 15, 2009, it is still only hypothetical or speculation that the intra-articular application of a catheter from a continuous flow pain pump medically causes glenhumeral chondrolysis, correct?
>
> A: *Well, that's a—correct statement and I can't argue with that.* But those are words and it makes it sound like we don't know what we're doing and that, gosh, guys, it might be all right for you to go and put this in because we're really not sure, and I—that isn't the case ...
>
> * * *
>
> Q: I understand that's your personal opinion, Dr. Poehling, but I'm asking you, on the general causation aspect, based on the available body of medical literature and science, this body of evidence that you talked about earlier in your response, would you agree with me, Dr. Poehling, that there is nothing in the available medical and scientific literature today as of May 15, 2009, which establishes causation between the intra-articular placement of a catheter that is part of a continuous flow pain pump and the condition of glenohumeral chondrolysis?
>
> ***9** A: Again, *you're specifically right* and I don't think I need to say what I feel otherwise.

Poehling Dep., at pp. 97:6–17; 99:7–19 (dkt # 72–2) (emphasis added). Poehling's concession that the current state of the medical literature is still unsettled about the cause of chondrolysis seriously undermines the reliability of his methodology. As Breg correctly notes, the Court cannot make up for the scientific leaps required to reach a conclusion on causation simply by viewing all of Kilpatrick's evidence as a whole:

> Conclusions and methodology are not entirely distinct from one another. Trained experts commonly extrapolate from existing data. But nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert. A court may conclude that there is

> simply too great an analytical gap between the data and the opinion proferred.

General Electric Co., 522 U.S. at 146, *overruling Joiner v. General Electric Co.,* 78 F.3d 524 (11th Cir.1996) (suggesting that evidence should be viewed "in its entirety" for *Daubert* purposes).

This Court has reviewed the studies Poehling claims to rely upon, and found that Poehling's extrapolations from them regarding causation are not warranted. What is more, Poehling, when pressed, essentially admits the same thing. Poehling's methodology has no known rate of error—to the extent one can be extrapolated from the Hansen study, it is an unexplained 40%—and at most, all he can offer is a hypothesis that "may be exactly right," but that right now is "merely plausible, not proven." *Accutane,* 511 F.Supp.2d at 1296. "[B]iological possibility is not proof of causation." *Id.* Under the circumstances, the Court would be derelict in the gatekeeping duties imposed on it by *Daubert* and Rule 702 if it found Poehling's testimony on general causation reliable.

d. *Poehling's Conclusions on Specific Causation are Also Unreliable*

To carry his burden on causation, Kilpatrick must show sufficient evidence of specific causation as well as general causation. *See McClain,* 401 F.3d at 1239. Kilpatrick's failure to present reliable evidence of general causation alone requires that Breg's *Daubert* motion be granted. However, Poehling's testimony about specific causation is also unreliable, because it is ultimately premised upon temporal relationship and the *post hoc ergo propter hoc* fallacy. "The *post hoc ergo propter hoc* fallacy assumes causation from temporal sequence. It literally means 'after that, because of this.' ... It is called a fallacy because it makes an assumption based on the false inference that a temporal relationship proves a causal relationship." *Id.* at 1243.

In describing how he concluded that Kilpatrick's chondrolysis was caused by the use of Breg's pain pump, Poehling described a process of differential diagnosis, ruling out other suspected causes of chondrolysis such as thermal energy and "gentian violet."[13] Poehling Dep., at pp. 85:21–87:21 (dkt # 72–2). Differential diagnosis means, in layman's terms, determining the cause of a disease by process of elimination.[14] Differential diagnosis "may offer an important component of a valid methodology" in determining specific causation, but it "will not usually overcome the fundamental failure of laying a scientific groundwork for the general toxicity of the drug ..." *McClain,* 401 F.3d at 1252–53. Ultimately then, because Poehling's testimony fails on the general causation prong, differential diagnosis does not suffice to carry Kilpatrick's burden on the specific causation prong.

13 The Parties describe gentian violet as a "contrast dye" that is sometimes injected into a patient's shoulder during arthroscopic surgery, but do not explain its purpose or function.

14 *See McClain,* 401 F.3d at 1252 ("Differential diagnosis involves 'the determination of which one of two or more diseases or conditions a patient is suffering from, by systematically comparing and contrasting their clinical findings.' ") (citations omitted). "The more precise but rarely used term is differential etiology ... [t]he etiology of a disease is the cause or origin of the disease ..." *Id.*

***10** However, even if Poehling's testimony satisfied the general causation inquiry, his conclusion on specific causation would still be unreliable for a more fundamental reason: it is ultimately rooted in nothing more than temporal relationship. It may be "almost irresistible to conclude that what happens shortly after the event must have been caused by the event," but that is not the basis of good science. *Accutane,* 511 F.Supp.2d at 1300. Yet this is precisely what Poehling does in describing his diagnosis of Kilpatrick's chondrolysis:

> ... I think any scientist would sit down and look at this case and *observe the factors of what happened to this patient, what he looked like before and what he looks like now* would come to the conclusion that bupivacaine is what caused it, and I don't think that that's just me or—I think any real scientist.

Poehling Dep., at p. 96:13–19 (dkt # 72–2) (emphasis added). Determining causation based on "what the patient looked like before" versus "what he looks like now" is the very definition of the *post hoc ergo propter hoc* fallacy. It is not a valid basis for scientific conclusions about specific causation, and Poehling's dependence upon it further weakens the reliability of his methodology.

e. *Kilpatrick Has Not Shown Any Other Valid Basis for Determining Causation*

As noted above, Kilpatrick points to various other articles that he claims provide evidence of the causation of chondrolysis, but when questioned during his deposition about medical literature that supports his conclusions, Poehling cited only the studies discussed above. *See* Poehling Dep., at pp. 43:20–45:10; 143:8–147:17 (dkt # 72–2). Breg correctly argues that where an expert witness is "unable to explain why these studies help inform her conclusion ... plaintiff's counsel cannot fill in the gaps." *In re Human Tissue Prods. Liability Litig.,* 582 F.Supp.2d 664, 667 (D.N.J.2008). A review of the literature that Poehling based his opinion on reveals that those articles do not support his conclusions without "leaps of faith" prohibited by Rule 702.

Kilpatrick points to some of Breg's internal documents to bolster his arguments on causation. However, neither Kilpatrick nor Poehling suggest that Poehling relied on these documents in reaching his conclusions, and they are therefore irrelevant to the *Daubert* inquiry. At most, Breg's documents, like the articles that Poehling relied upon, mention an association between pain pumps an chondrolysis, which, as discussed, is not equivalent to causation. *See Accutane,* 511 F.Supp.2d 1288 (excluding expert testimony where expert claimed to have relied on defendant's internal documents in reaching conclusions on causation; if defendant's documents had admitted causation, "this Court could have saved a lot of time—this opinion would have been unnecessary.").

B. *Breg's Motion for Summary Judgment*

1. *Standard of Review*

***11** The applicable standard for reviewing a summary judgment motion is unambiguously stated in Rule 56(c) of the Federal Rules of Civil Procedure:

> The judgment sought should be rendered if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law.

Summary judgment may be entered only where there is no genuine issue of material fact. *Twiss v. Kury,* 25 F.3d 1551, 1554 (11th Cir.1994). The moving party has the burden of meeting this exacting standard. *Adickes v. S.H. Kress & Co.,* 398 U.S. 144, 157, 90 S.Ct. 1598, 26 L.Ed.2d 142 (1970). An issue of fact is "material" if it is a legal element of the claim under the applicable substantive law which might affect the outcome of the case. *Allen v. Tyson Foods, Inc.,* 121 F.3d 642, 646 (11th Cir.1997). An issue of fact is "genuine" if the record taken as a whole could lead a rational trier of fact to find for the nonmoving party. *Id.*

In applying this standard, the district court must view the evidence and all factual inferences therefrom in the light most favorable to the party opposing the motion. *Id.* However, the nonmoving party "may not rely merely on allegations or denials in its own pleading; rather, its response must—by affidavits or as otherwise provided in this rule—set out specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e)(2). "The mere existence of a scintilla of evidence in support of the [nonmovant's] position will be insufficient; there must be evidence on which the jury could reasonably find for the [nonmovant]." *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 252, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986)

2. *Causation*

Causation is an element common to all of Kilpatrick's claims. To sufficiently establish causation for a negligence claim in a products liability action, the plaintiff bears the burden of proving by a preponderance of the evidence that his injury was proximately caused by the manufacturer's breach of its duty to produce a product reasonably safe for use. *See Indem. Ins. Co. of N. Am. v. Am. Aviation, Inc.,* 344 F.3d 1136, 1146 (11th Cir.2003) (applying Florida law). To prove causation under a strict products liability theory, the plaintiff bears the burden of proving that the product defect proximately caused his injury. *See McCorvey v. Baxter Healthcare Corp.,* 298 F.3d 1253, 1257 (11th Cir.2002) (citing *Edward M. Chadbourne, Inc. v. Vaughn,* 491 So.2d 551, 553 (Fla.1986)). Causation is also one of the elements of a claim arising under the Florida Deceptive and Unfair Trade Practices Act. *See City First Mortg. Corp. v. Barton,* 988 So.2d 82, 86 (Fla. 4th Dist.Ct.App.2008) (elements of FDUTPA claim are deceptive act or unfair practice, causation, and actual damages) (citations omitted).

Kilpatrick's failure to proffer sufficient evidence of causation, an element critical to all of his claims, is necessarily fatal to his efforts to avoid summary judgment. *See Rink,* 400 F.3d at 1294–96 (affirming grant of summary judgment where plaintiff's expert evidence was unreliable to prove causation); *Allison,* 184 F.3d at 1320 (same). Poehling is Kilpatrick's sole designated expert on the issue of causation. Kilpatrick's only other possible source of evidence on causation is the testimony of Kilpatrick's two treating physicians, Papilion and Uribe. Treating physicians not offered as experts, however, may only testify as lay witnesses to matters within the scope of their own personal observation, such as treatment. *See U.S. v. Henderson,* 409 F.3d 1293, 1300 (11th Cir.2005) (treating physician impermissibly offered expert testimony on causation, where determining causation was not necessary to either diagnosis or treatment). Because Uribe and Papilion have neither been designated as experts nor completed expert reports pursuant to Federal Rule of Civil Procedure 26, their testimony would necessarily be limited to matters of personal observation and cannot touch upon causation. *See, e.g., Widhelm v. Wal–Mart Stores, Inc.,* 162 F.R.D. 591, 594 (D.Neb.1995) (treating physicians not required to complete expert report to offer expert testimony on treatment, but plaintiffs' attempts "to solicit expert testimony about causation ... will not be permitted"). In the absence of any reliable expert evidence on causation, summary judgment must be granted in favor of Breg.

III. CONCLUSION

***12** Based on the foregoing, it is

ORDERED AND ADJUDGED that Breg's Motion to Exclude Causation Testimony (dkt # 71) is GRANTED. It is further

ORDERED AND ADJUDGED that Breg's Motion for Summary Judgment (dkt # 69) is GRANTED. The Clerk of Court is directed to CLOSE this case. All pending motions not otherwise ruled upon are DENIED AS MOOT.

DONE AND ORDERED.

All Citations

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2006 WL 1529582
United States District Court,
S.D. Indiana, Terre Haute Division.

Mickey ERVIN, Plaintiff,
v.
JOHNSON & JOHNSON, INC.
and Centocor, Inc., Defendants.

No. 2:04CV0205-JDT-WGH.
|
May 30, 2006.

Attorneys and Law Firms

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ENTRY ON DEFENDANTS' MOTION FOR SUMMARY JUDGMENT (Docket No. 39) AND MOTION IN LIMINE TO EXCLUDE EXPERT TESTIMONY (Docket No. 43), AND ON PLAINTIFF'S MOTION TO EXCLUDE EXPERT TESTIMONY (Docket No. 40) [1]

1 This Entry is a matter of public record and will be made available on the court's web site. However, the discussion contained herein is not sufficiently novel to justify commercial publication.

TINDER, J.

***1** Plaintiff Mickey Ervin brought this product liability suit against the Defendants, Johnson & Johnson, Inc. ("Johnson & Johnson") and Centocor, Inc. ("Centocor"), alleging that Remicade, a drug developed by Defendants to treat Crohn's disease, caused Ervin to develop an arterial blood clot, which led to the amputation of his lower leg. The Defendants filed a motion for summary judgment and a corresponding motion in limine to exclude the testimony of Dr. Lee McKinley, who is the Plaintiff's medical expert. The Plaintiff likewise filed a motion to exclude portions of the testimonies of Drs. Douglas Rex and Barbara Matthews, who are the Defendants' medical experts. These motions are now ripe for review, and the court finds as follows:

I. BACKGROUND

In March 2001, Ervin was a twenty-year-old male suffering from Crohn's disease, Type 1 insulin dependent diabetes, and hypothyroidism. (McKinley Dep. 26:1-11.) His case of Crohn's was severe, and he required over 200 units of blood transfusions over a period of years prior to March 2001 due to the disease. (Ghosh Dep. 40:12-41:1; McKinley Dep. 34:20-36:3.) Ervin received several different medications to treat his Crohn's disease, but none were very effective in treating his disease.

In March 2001, Dr. Maisel, Ervin's gastroenterologist, discussed with Ervin the option of treating his Crohn's with Remicade. (Maisel Dep. 23:10-13.) At the time of the discussion, Dr. Maisel was familiar with the possible risks and side effects associated with Remicade, including the information that was listed on the drug's package insert. (*Id.* at 34:9-35:1.) The package insert stated the following:

> ADVERSE REACTIONS:
>
> Serious adverse events (all occurred at frequencies <2%) by body system in all patients treated with REMICADE are as follows:
>
> ...
>
> *Vascular (Extracardiac):* brain infarction, peripheral ischemia, pulmonary embolism, *thrombophlebitis deep.*

(S.J. Br., Ex. 8 (emphasis added).) "Thrombophlebitis deep" refers to the risk of venous thrombosis, not arterial thrombosis. Ervin agreed to the treatment and underwent his first infusion of Remicade on March 21, 2001. Ervin had no problems with the first infusion. (Maisel Dep. at 28:1-3.) He underwent a second infusion of Remicade on April 25, 2001. During this second infusion, Ervin experienced certain syptoms and the infusion was stopped temporarily so a nurse could treat him with Benadryl. (*Id.* at 30:15-31:3.) The symptoms dissipated, and Ervin completed the second infusion and was discharged without complications. (*Id.* at 31:12-17.)

On April 30, 2001, Ervin complained to his internal medicine doctor, Dr. McKinley, of pain in his hands and legs. After examining Ervin, Dr. McKinley adjusted his diabetes medication and prescribed a pain medication. (McKinley Dep. 66:20-67:12.) After the pain intensified, Ervin was hospitalized the next day, on May 1, 2001. The doctors diagnosed him with arterial thrombosis (a blood clot located in the artery) of the left leg. Dr. Morrison, a vascular surgeon, performed a thromboembolectomy on May 1 to clear the clot and restore the blood flow. Initially, the procedure appeared successful, but on May 4, just prior to his scheduled discharge, Ervin experienced additional arterial thrombosis in his left leg. Additional attempts to clear the clots failed, and Ervin underwent a left below-the-knee amputation on May 6, 2001.

***2** Lab reports taken during his hospitalization in May 2001 show that Ervin had a Protein S activity level of 61%. (Mot. Limine Br., Ex.14.) Protein S is a naturally occurring anticoagulant-a low Protein S level is indicative of a higher tendency to clot. (Morrison Dep. 13:16-20.) The lab report defined 61% as "Low." However, Dr. McKinley asserts that a Protein S activity level above 50% is not clinically significant.

In addition to low Protein S activity and Crohn's disease, Ervin also registered an elevated platelet count of 674,000. While this number is elevated, Dr. McKinley stated that it is not "into the range that we would actively treat it." (McKinley Dep. 57:24-25.) In addition, Dr. McKinley noted that Ervin had at least a four-year history of elevated platelet counts. (*Id.* at 57:17-20.)

In May 2002, one year after his arterial thrombosis and subsequent amputation, Ervin developed a cerebral vein thrombosis. Ervin had not undergone any Remicade treatments since the previous incident and the cerebral vein thrombosis was completely unrelated to Remicade. (*Id.* at 156:19-25.) In July 2002, one month after the cerebral thrombosis, lab reports indicated that his Protein S level was at 33% (Mot. Limine Br., Ex.15), which, according to Dr. McKinley, was significantly low (McKinley Dep. 84:11-14).

The Food and Drug Administration ("FDA") approved Remicade for use with Crohn's disease in August 1998 and for use with rheumatoid arthritis in November 1999. Centocor submits the Remicade Periodic Safety Update Reports ("PSUR") to the FDA and the European Medicines Agency on a biannual basis. In each report, Centocor provides information on thromboembolic events reported during the relevant six-month period and assesses possible causal associations. The PSURs indicate that, as of August 23, 2003, 492,874 patients had been exposed to Remicade. (PSUR (8), Feb. 2003-Aug.2003, pg. 1.) Of those 492,874 patients, Centocor had received 356 reports of thromboembolic events (0.072%), which include both arterial and venous events. [2] (PSUR (9), Aug. 2003-Feb.2004, pg. 152.) There had only been twenty-nine reported cases (0.006%) of arterial thrombosis with those patients. (*Id.*) These figures demonstrate a 0.006% reported occurrence rate of arterial thrombosis with those patients exposed to Remicade.

2 The February 2004 PSUR (9) indicates that there have been a total of 408 reported thromboembolic events. Because PSUR (9) does not provide a total patient exposure number as of February 2004, the court will use the total patient exposure number of 492,874 that is indicated in the August 2003 PSUR (8). Thus, the court will subtract the thromboembolic events indicated in PSUR (9) that occurred after PSUR (8).

Medical studies and case reports have linked vascular complications and thrombosis to patients with Crohn's disease. One study followed 7199 Crohn's patients over an eleven year period at the Mayo Clinic. Robert W. Talbot et al., *Vascular Complications of Inflammatory Bowel Disease,* 61 Mayo Clin. Proc. 140 (1986). Of those 7199 patients, ninety-two developed a thromboembolic condition (1.3%). *Id.* However, only seven of those ninety-two cases involved arterial thrombosis (0.1%). *Id.* at 142. Moreover, six of the seven arterial thrombosis cases involved postoperative patients. *Id.* Thus, only one non-postoperative Crohn's patient in the study developed a case of arterial thrombosis (0.014%). Another study completed in 1936 reports that eighteen of 1500 Crohn's patients (1.2%) developed extensive arterial and venous thrombosis. *Id.* at 140. Although the court cannot tell how many of those eighteen reported cases involved arterial thrombosis, it can infer that there was at least one case of arterial thrombosis as part of that study. Nevertheless, the extremely low occurrence rate of arterial thrombosis in these studies suggests that it is a rare event that occurs in anywhere from 0.014% to 0.1% of Crohn's patients.

II. STANDARD OF REVIEW

***3** The purpose of summary judgment is to "pierce the pleadings and to assess the proof in order to see whether there is a genuine need for trial." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.,* 475 U.S. 574, 587, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). Summary judgment is appropriate where the pleadings, depositions, answers to interrogatories, affidavits, and other materials demonstrate that there exists "no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c). The court considers those facts that are undisputed and views additional evidence, and all reasonable inferences drawn therefrom, in the light most reasonably favorable to the nonmoving party. *See Celotex Corp. v. Catrett,* 477 U.S. 317, 323, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986); *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 255, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986); *Baron v. City of Highland Park,* 195 F.3d 333, 337-38 (7th Cir.1999). However, once a properly supported motion for summary judgment is made, the non-movant "cannot rest on the pleadings alone, but must identify specific facts to establish that there is a genuine triable issue." *Donovan v. City of Milwaukee,* 17 F.3d 944, 947 (7th Cir.1994); *see* Fed.R.Civ.P. 56(e).

III. DISCUSSION

A. Fact of Causation May be Established by Expert Testimony Only

Ervin brings five counts against the Defendants: 1) Product Liability-Negligence; 2) Product Liability-Failure to Warn; 3) Breach of Warranty of Merchantability; 4) Wantonness; and 5) Fraud, Misrepresentation, and Suppression. Ervin does not dispute that each of his claims requires a finding of fact that the Defendants' Remicade was the legal cause of his arterial thrombosis and subsequent amputation. "Proximate cause is an essential element of, and is determined in the same manner in, both negligence and product liability actions." *Wolfe v. Stork RMS-Protecon, Inc.,* 683 N.E.2d 264, 268 (Ind.Ct.App.1997). Without a proved causal relationship, all causes of action connecting Ervin's arterial thrombosis to Remicade fail for lack of an essential element. Ervin's product liability claims place upon the claimant the burden of proving that "the defective condition was a proximate cause of the loss complained of." *Lantis v. Astec Indus., Inc.,* 648 F.2d 1118, 1120 (7th Cir.1981) (applying Indiana law); *Ortho Pharm. Corp. v. Chapman,* 180 Ind.App. 33, 388 N.E.2d 541, 545 (Ind.Ct.App.1979). A party claiming injury bears the burden of proving an injury proximately resulting from the defendant's acts. *Harris v. Raymond,* 715 N.E.2d 388, 393 (Ind.1999); *Cowe by Cowe v. Forum Group,* 575 N.E.2d 630, 636 (Ind.1991). Ervin must prove that the Defendants' Remicade caused his injury.

Proximate cause requires a showing of causation in fact, which is a showing that "the injury would not have occurred without the defendant's negligent act or omission." *City of Gary ex rel. King v. Smith & Wesson Corp.,* 801 N.E.2d 1222, 1243-44 (Ind.2003); *see also Ortho Pharm.,* 388 N.E.2d at 555 (A legal cause-in-fact is "that cause which, in natural and continuous sequence, unbroken by any efficient intervening cause, produced the result complained of and without which the result would not have occurred."). "At a minimum, proximate cause requires that the injury would not have occurred but for the defendant's conduct." *Paragon Family Rest. v. Bartolini,* 799 N.E.2d 1048, 1054 (Ind.2003); *see also Hamilton v. Ashton,*-N.E.2d-, 846 N.E.2d 309, 2006 WL 1098288, at *5 (Ind.Ct.App. Apr.27, 2006). Under Indiana law, the evidentiary standard required to establish the fact of causation in this matter is a preponderance of the evidence, which requires a "more likely than not" showing. *Watson v. Med. Emergency Serv. Corp.,* 532 N.E.2d 1191 (Ind.Ct.App.1989). Ervin must prove by a preponderance of the evidence that his arterial thrombosis would not have occurred but for his Remicade infusion.

***4** "When the issue of proximate cause is not within the understanding of lay persons, testimony of an expert witness on the issue is necessary." *Watson,* 532 N.E.2d at 1194. Due to the medical issues involved in this case, the matter presents a situation where expert testimony is not only helpful but absolutely necessary. Under Indiana law, "questions of medical causation of a particular injury are questions of science necessarily dependent on the testimony of physicians and surgeons learned in such matters." *Armstrong v. Cerester USA, Inc.,* 775 N.E.2d 360, 366 (Ind.Ct.App.2002) (quoting *Hannan v. Pest Control Servs., Inc.,* 734 N.E.2d 674, 679 (Ind.Ct.App.2000)). Accordingly, the Defendants' motion to exclude Dr. McKinley's expert testimony on causation is a watershed issue. If Dr. McKinley's expert testimony is inadmissible, then Ervin lacks expert testimony on the issue of medical causation, and summary judgment in favor of the Defendants would be appropriate.

B. Expert Testimony of Dr. McKinley

For an expert's testimony to be admissible, it must comport with the requirements of Federal Rule of Evidence 702 and the Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). The Seventh Circuit recently reemphasized that "Rule 702 has superseded *Daubert,* but the standard of review that was established for *Daubert* challenges is still appropriate." *United States v. Parra,* 402 F.3d 752, 758 (7th Cir.2005).

Rule 702 and *Daubert* require that the court determine whether the expert testimony is both relevant and reliable. In determining reliability, the court must ascertain whether the expert is qualified in the relevant field and whether the methodology underlying the expert's conclusions is reliable. *Zelinski v. Columbia 300, Inc.,* 335 F.3d 633, 640 (7th Cir.2003) (citing *Smith v. Ford Motor Co.,* 215 F.3d 713, 718 (7th Cir.2000)). Thus, the court must undertake a three-step analysis in determining whether expert testimony is admissible under Rule 702. First, the witness must be qualified "as an expert by knowledge, skill, experience, training, or education." Fed.R.Evid. 702. Second, the expert's reasoning or methodology underlying the testimony must be scientifically reliable. *Daubert,* 509 U.S. at 592-93. Finally, the testimony must "assist the trier of fact to understand the evidence or to determine a fact in issue." Fed.R.Evid. 702. The court will apply this three-step analysis to the expert testimony of Dr. McKinley.

The Defendants first argue that Dr. McKinley lacks the requisite "knowledge, skill, experience, training, or education" under Rule 702 to qualify as an expert to give testimony on the causal relationship between Remicade and Ervin's arterial thrombosis. The Defendants aver, and Ervin does not dispute, that Dr. McKinley is not an expert in epidemiology or biostatistics. (McKinley Dep. 50:6-9.) Likewise, he is not a gastroenterologist and has never prescribed Remicade. However, Dr. McKinley is a practicing board certified internal medicine and critical care specialist. He has experience treating patients with Crohn's disease. (*Id.* 41:6-8.) As a practicing internist, he often uses the process of differential diagnosis to make diagnostic and therapeutic decisions for patient care. (McKinley Expert Report 2.) In addition, he lectures on thrombophilia (McKinley Dep. 136:12-13), which is "a disorder of the hemopoietic system in which there is a tendency to the occurrence of thrombosis." *Stedman's Medical Dictionary* 1831 (27th ed.2000). For the last sixteen years, he has taught medical and doctoral students at the Indiana University campus their initial lectures on clinical coagulation (clotting) disorders. (McKinley Dep. 136:17-23.) This experience gives Dr. McKinley the requisite knowledge, training, skill, and education to provide an expert opinion, based upon a differential diagnosis, regarding the cause of Ervin's arterial thrombosis.

***5** Once the expert is deemed qualified, the court must address whether the methodology underlying the expert's conclusion is reliable. *See Ammons v. Aramark Uniform Servs., Inc.,* 368 F.3d 809, 816 (7th Cir.2004). It is not the court's role to decide whether an expert testimony is correct; instead, the court performs a gatekeeping function in which it is "limited to determining whether expert testimony is pertinent to an issue in the case and whether the methodology underlying that testimony is sound." *Smith,* 215 F.3d at 719 (citation omitted). In determining whether the "reasoning or methodology underlying the testimony is scientifically valid," *Daubert,* 509 U.S. at 592-93, the court must consider "whether the testimony has been subjected to the scientific method, ruling out any subjective belief or unsupported speculation." *Chapman v. Maytag Corp.,* 297 F.3d 682, 687 (7th Cir.2002) (citing *Porter v. Whitehall Labs. Inc.,* 9 F.3d 607, 614 (7th Cir.1993)).

In this case, Dr. McKinley relies on the process of differential diagnosis to arrive at his opinion, concluding that "to a reasonable degree of medical certainty ... the use of the Remicade was the major contributing factor to Mr. Ervin's thrombotic arterial occlusion and subsequent below knee amputation." (McKinley Expert Report 3.) Differential diagnosis, or differential etiology, is a process by which a physician determines the cause of a patient's symptoms by first determining, or "ruling-in," all plausible causes for the patient's symptoms and then eliminating each of these potential causes until reaching one that cannot be ruled out or determining which of those that cannot be excluded is the most likely. This technique "has widespread acceptance in the medical community, has been subject to peer review, and does not frequently lead to incorrect results." *In re Paoli R.R. Yard PCB Litig.,* 35 F.3d 717, 758 (3d Cir.1994). While the Seventh Circuit has not directly addressed whether a proper differential diagnosis can satisfy Rule 702 and *Daubert,* the majority of the courts of appeals has recognized the technique as valid and reliable. *See*

Feliciano-Hill v. Principi, 439 F.3d 18, 25 (1st Cir.2006) (finding that differential diagnosis is a reliable technique under *Daubert*); *Bitler v. A.O. Smith Corp.,* 391 F.3d 1114, 1123-1124 (10th Cir.2004) (finding that differential diagnosis is "a common method of analysis" and is reliable under *Daubert*); *Clausen v. M/V New Carissa,* 339 F.3d 1049, 1058-59 (9th Cir.2003) (recognizing differential diagnosis as a reliable method); *Mattis v. Carlon Elec. Prods.,* 295 F.3d 856, 861 (8th Cir.2002) (holding that "[a] medical opinion based upon a proper differential diagnosis is sufficiently reliable to satisfy *Daubert"*); *Hardyman v. Norfolk & W. Ry. Co.,* 243 F.3d 255, 261 (6th Cir.2001) (recognizing differential diagnosis as an acceptable method of determining causation); *Westberry v. Gislaved Gummi AB,* 178 F.3d 257, 262 (4th Cir.1999) (holding that differential diagnosis is a reliable technique "of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated"); *Zuchowicz v. United States,* 140 F.3d 381, 387 (2d Cir.1998) (upholding district court decision to admit differential diagnosis testimony); *In re Paoli,* 35 F.3d at 758 (same). *But see Rink v. Cheminova, Inc.,* 400 F.3d 1286, 1295 (11th Cir.2005) (holding that in the context of summary judgment, differential diagnosis evidence by itself does not suffice for proof of causation).

***6** However, while these courts recognize the methodology of differential diagnosis as scientifically valid, the same courts also warn that opinions based on differential diagnosis must be analyzed on a case-by-case basis, ensuring that the expert's application of the technique is reliable and proper in each case. As the Eleventh Circuit explained:

> [A]n expert does not establish the reliability of his techniques or the validity of his conclusions simply by claiming that he performed a differential diagnosis on the patient.... "No one doubts the utility of medical histories in general or the process by which doctors rule out some known causes of disease in order to finalize a diagnosis. But such general rules must ... be applied fact-specifically in each case."

McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1253 (11th Cir.2005) (quoting *Black v. Food Lion, Inc.,* 171 F.3d 308, 314 (5th Cir.1999)); *see also In re Paoli,* 35 F.3d at 758 (Differential diagnosis "is a method that involves assessing causation with respect to a particular individual. As a result, the steps a doctor has to take to make that (differential) diagnosis reliable are likely to vary from case to case.") Thus, an expert's use of differential diagnosis is reliable and valid only if the expert applied the technique in a manner which is also reliable. In this case, the court finds two critical flaws in the manner in which Dr. McKinley applied the differential diagnosis. Due to these flaws, the diagnosis itself is not sufficiently reliable to satisfy *Daubert.*

1. *Flaw in Rule-In Aspect of Differential Diagnosis*

In a proper differential diagnosis, the physician's first step is to "rule-in" all of the scientifically plausible causes for the patient's symptoms. This step of the diagnosis includes the general causation aspect of the test. In other words, in order to rule-in a plausible cause, the expert must first reach the determination that the suspected cause is actually capable of causing the injury. Expert opinion on the issue of general causation must be derived from a scientifically valid methodology. In this case, Dr. McKinley rules-in Remicade as a plausible cause for the arterial thrombosis, and, in doing so, finds that Remicade is actually capable of causing the arterial thrombosis. Dr. McKinley provides no epidemiological studies linking Remicade to arterial thrombosis and provides no physiological explanation as to how Remicade would cause arterial thrombosis. Instead, he bases the ruling-in (or general causation) aspect of his opinion on the temporal proximity between the infusion of the drug and the development of the clot, and upon a limited number of case reports, which were reported in the manufacturer's Periodic Safety Update Reports (PSUR) to the FDA, that also demonstrate a temporal proximity.

Courts should treat with caution those expert opinions based on case reports. As one court explained, "case reports are merely accounts of medical events." *Rider v. Sandoz Pharms. Corp.,* 295 F.3d 1194, 1199 (11th Cir.2002). A doctor makes a case report when a patient demonstrates adverse symptoms that are temporally connected with the prescribed drug. The reports contain very basic information, often omitting patient histories, descriptions of the course of treatment, and reasoning to exclude other possible causes. "Case reports make little attempt to screen out alternative causes for a patient's condition. They frequently lack analysis. And they often omit relevant facts about the patient's condition. Hence, 'causual attribution based on case studies must be regarded with caution." ' *Glastetter v. Novartis Pharms. Corp.,* 252 F.3d 986, 989-90 (8th Cir.2001) (quoting

Reference Manual on Scientific Evidence 475 (Federal Judicial Center 2000)); see also *Rider,* 295 F.3d at 1199 (affirming the district court's exclusion of expert testimony based on case reports because "they do not rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors"); *Hollander v. Sandoz Pharms. Corp.,* 289 F.3d 1193, 1209-12 (10th Cir.2002) (same); *Meister v. Med. Eng'g Corp.,* 267 F.3d 1123, 1129 (D.C.Cir.2001) (same); *Caraker v. Sandoz Pharms. Corp.,* 188 F.Supp.2d 1026, 1035 (S.D.Ill.2001) (same); *Lennon v. Norfolk & W. Ry. Co.,* 123 F.Supp.2d 1143, 1152-53 (N.D.Ind.2000) (same). Indeed, Dr. McKinley agrees that a doctor should not rely merely on case studies to establish a causal relationship. (McKinley Dep. 129:11-18, 130:20-23.) In essence, the case reports do little more than establish a temporal association between an exposure to a drug and a particular occurrence. Granted, "an overwhelming amount of case reports of a temporal proximity between a very specific drug and a very specific adverse event might be enough to make a general causation conclusion sufficiently reliable." *Caraker,* 188 F.Supp.2d at 1035. Here, Dr. McKinley believed he saw "enough" occurrences of arterial thrombosis in these case reports to justify ruling-in Remicade as a plausible cause of the arterial thrombosis. (McKinley Dep. 129:12-23.)

***7** Despite Dr. McKinley's concerns, the case reports show a relatively small number of occurrences of arterial thrombosis. As of August 23, 2003, 492,874 patients had been exposed to Remicade. (PSUR (8), 2/03-8/03, pg. 1.) Of those 492,874 patients, there had only been twenty-nine case reports indicating arterial thrombosis (PSUR (9), 8/03-2/04, pg. 152).[3] Again, very little is known about these twenty-nine incidents or about possible contributing factors. Even so, twenty-nine occurrences out of 492,874 patients results in a percentage of 0.006%. This low figure does not appear to justify ruling in Remicade as a plausible cause. But even if it does, then Dr. McKinley should have also considered, or ruled-in, Ervin's Crohn's disease as a plausible cause of the arterial thrombosis.

3 The February 2004 PSUR (9) actually indicates that there have been a total of 30 reported arterial thrombosis. However, PSUR (9) does not provide a total patient exposure number as of February 2004, so the court will use the total patient exposure number of 492,874 that is indicated in the August 2003 PSUR (8). In doing so, the court will also subtract the arterial thrombosis events indicated in PSUR (9) that occurred after PSUR (8), which was just one additional case of arterial thrombosis.

Ervin suffers from a severe case of Crohn's. Prior to the Remicade treatments, his Crohn's was so severe that Ervin required two to three blood transfusions every two weeks. (McKinley Dep. 58:4-6.) Case studies have also shown a temporal relationship between Crohn's disease and arterial thrombosis. One peer-reviewed article describes a case study of 7199 patients with Crohn's disease at the Mayo Clinic from 1970 to 1980. Robert W. Talbot et al., *Vascular Complications of Inflammatory Bowel Disease,* 61 Mayo Clin. Proc. 140 (1986). Of those 7199 patients, seven developed arterial thrombosis, which results in a percentage of 0.1%. *Id.* at 142. Dr. McKinley qualifies this number by observing that six of these seven occurrences were with post-operative patients.[4] Even if the six post-operative occurrences were not considered, then the study still shows that one out of 7199 Crohn's patients (0.014%) in the case study developed an arterial thrombosis. This is admittedly a low figure, and for that reason, Dr. McKinley will not rule-in Crohn's as a plausible cause in his differential diagnosis. The court understand's Dr. McKinley's reasoning for not ruling in Crohn's with the case study demonstrating such a low occurrence. However, what the court does not understand and what most concerns the court is that Dr. McKinley has no problem ruling-in Remicade, with an occurrence rate of 0.006% in the case reports, but refuses to rule-in Crohn's because its occurrence rate of 0.014% to 0.1% is too low. The decision to rule-in Remicade is not only based on unreliable data demonstrating an insignificant occurrence rate, but it is also inconsistent with his decision not to rule-in Crohn's. Thus, the court finds that his application of the differential diagnosis technique is unreliable and fails the standards set forth in Rule 702 and *Daubert.*[5]

4 The court notes that due to the limited information available in the case reports regarding the twenty-nine occurrences of arterial thrombosis associated with Remicade, the court does not know how many of those twenty-nine patients were also post-operative. This fact illustrates the problem with relying on case reports in support of a medical opinion.

5 In addition, Dr. McKinley appears to call into doubt his own opinion. When confronted with scientific medical literature associating arterial thrombosis with Crohn's disease and asked how that information would affect his opinion, he admits that in 2001, he

> did not know of an association between Crohn's and thrombosis, and that now "I am aware there are more cases [associating Crohn's with arterial thrombosis] out there than there were then [in 2001]. I wish I had known those things then. I didn't.... I would have to reinterpret this case in a completely different way.... I have to look at the way I thought then and I could probably look at the way I could think now." (McKinley Dep. 98:18-102:19.) In forming his opinion, Dr. McKinley should consider all evidence, including evidence he has learned since the time of the injury in May 2001. He does not appear to do so here.

2. *Flaw in Rule-Out Aspect of Differential Diagnosis*

After properly ruling-in all of the plausible causes of the patient's symptoms, the physician's next step in the differential diagnosis is to eliminate, or "rule-out," each of these potential causes until reaching one that cannot be ruled out or determining which of those that cannot be excluded is the most likely. This step of the diagnosis includes the specific causation aspect of the test. In this case, Dr. McKinley ruled-in multiple plausible causes (but, as explained above, failed to rule-in Crohn's), including deficient Protein S levels, viscosity of the blood, elevated platelet count, vasculitis, and Remicade. (McKinley Dep. 96:5-25.) Dr. McKinley was able to rule-out each of these plausible causes, except for Remicade. Accordingly, he opines that Remicade was the most likely cause of the arterial thrombosis.

***8** Dr. McKinley ruled-out the possibility that a low Protein S activity level could have caused the arterial thrombosis. Protein S is a naturally occurring anticoagulant-when it is low, the blood has a higher tendency to clot. Lab reports taken during Ervin's hospitalization in May 2001 show that he had a Protein S activity level of 61%. (Mot. Limine Br., Ex. 14.) The lab report defined 61% as "Low." However, Dr. McKinley asserts that a Protein S activity level above 50% is not clinically significant. (McKinley Dep. 84:11-14.) In addition, Dr. McKinley recognized that a deficient Protein S level is "only associated with venous disease," and is not pertinent to arterial disease. (*Id.* 85:18-23.) Because his level was not significantly low and because he had suffered an arterial event, Dr. McKinley ruled-out low Protein S as the specific cause of Ervin's arterial thrombosis.

A problem arises in Dr. McKinley's reasoning because, as noted in one medical textbook, "[a]rterial thrombosis seems to occur more frequently in subjects with [Protein S] deficiency than in other thrombophilic states." Scott H. Goodnight & William E. Hathaway, *Disorders of Hemostasis and Thrombosis* 377-78 (2001). Upon further questioning, even Dr. McKinley concedes that he is aware of some rare reports associating protein S deficiencies with arterial disease. (McKinley Dep. 85:23-86:4.) Furthermore, in May 2002, one year after his arterial thrombosis and subsequent amputation, Ervin developed a cerebral vein thrombosis. Ervin had not undergone any Remicade treatments since the previous incident and the cerebral vein thrombosis was completely unrelated to Remicade. (*Id.* 156:19-25.) In July 2002, one month after the cerebral thrombosis, lab reports indicated that his Protein S level was at 33% (Mot. Limine Br., Ex.15), which, according to Dr. McKinley, was significantly low (McKinley Dep. 84:11-14). Despite the fact that the significantly low Protein S level in 2002 could be indicative of some type of thromboembolic potential (*Id.* 105:20-24), Dr. McKinley nevertheless did not include the 2002 level in considering whether a low Protein S level could had played a part in his 2001 arterial thrombosis. But he concedes that if he were to form an opinion today, including consideration of the 2002 Protein S level, he "would have to add this to the list of possibilities." (*Id.* 106:8-9.)

Dr. McKinley admits that a significantly low Protein S level has been associated, at least in some cases, with arterial thrombosis. He further admits that Ervin's significantly low Protein S level in 2002 could be indicative of a hypercoagulability syndrome (*Id.* 107:2-4), which should also be added to the list of plausible causes. He provides no reason to rule-out this plausible cause (at least not with the 2002 Protein S levels). Accordingly, Dr. McKinley's differential diagnosis fails to demonstrate how Remicade is a more likely cause than a low Protein S level.

***9** The flaws in Dr. McKinley's differential diagnosis, as explained above, leave his diagnosis unreliable under the standards set forth in Rule 702 and *Daubert*.[6] As such, the court will GRANT the Defendants motion in limine and exclude the expert testimony of Dr. McKinley. Ervin has no other expert testimony on the issue of medical causation and each of his counts against the Defendants will fail for lack of satisfying the requisite causation element. Accordingly, the Defendants are entitled to summary judgment on all counts.

6 These same considerations would have also precluded Dr. McKinley's opinion at the third step of the Rule 702 analysis in that his inadequate analysis would not have aided the jury in understanding the causation question or in determining whether Remicade was the cause of the arterial thrombosis. Without repeating the discussion above, Dr. McKinley's conclusions would have only justified speculation on the part of the jurors as to causation and would not have provided a sound basis for a decision in the Plaintiff's favor.

IV. CONCLUSION

For the foregoing reasons, the court GRANTS the Defendants' motion in limine to exclude the expert testimony of Dr. McKinley (Docket No. 43), and GRANTS the Defendants' motion for summary judgment (Docket No. 39). Because the Defendants are entitled to summary judgment, the Plaintiff's motion to exclude aspects of the Defendants' expert witnesses' opinions (Docket No. 40) need not be addressed. It therefore is DENIED AS MOOT. The court directs the Clerk to enter judgment in favor of the Defendants Centocor and Johnson & Johnson.

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